Short-term Effects of Particulate Matter Pollutants on Population Health - Time Series Studies on Emergency Hospital Admissions

QIU, Hong

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy
in
Social Medicine

The Chinese University of Hong Kong
September 2012

顆粒污染物對人群健康的短期效應
——時間序列研究

邱 宏

社會醫學課程

哲學博士論文

香港中文大學

2012 年 6 月

Thesis/Assessment Committee

Professor Zee Benny Chung Ying (Chair)

Professor Yu Ignatius Tak Sun (Thesis Supervisor)

Professor Wang Xiaorong (Thesis Supervisor)

Professor Hui David Shu Cheong (Committee Member)

Professor Samet Jonathan M. (External Examiner)

論 文 評 審 委 員 會

徐仲錂教授（主席）

余德新教授（論文導師）

王曉蓉教授（論文導師）

許樹昌教授（委員）

Samet JM 教授（校外委員）

Abstract (English)

Abstract of thesis entitled:	Short-term Effects of Particulate Matter Pollutants on Population Health --- Time Series Studies on Emergency Hospital Admissions
Submitted by	QIU Hong
for the degree of	Doctor of Philosophy
at the Chinese University of Hong Kong (June 2012)	

BACKGROUND: The adverse effects of particulate matter (PM) air pollution have been confirmed by many epidemiological studies. Fine and coarse particles should be considered as separate classes of pollutants and measured separately. Differentiating the effects of fine ($PM_{2.5}$, particles with an aerodynamic diameter less than 2.5 microns) and coarse particles (PM_c, particles with an aerodynamic diameter between 2.5 and 10 microns) would help in the future to support a PM_c standard. Meanwhile, ambient air pollution is a complex mixture of PM and gaseous pollutants. PM might interact with gaseous pollutants to affect the population health.

STUDY OBJECTIVES: To differentiate the effects of fine and coarse fractions of PM_{10} and to explore the possible interaction between PM_{10} and gaseous pollutants (nitrogen dioxide, NO_2; sulfur dioxide, SO_2; ozone, O_3) on emergency hospital admissions for cardio-respiratory diseases in Hong Kong.

METHODS: This is a time series study. Daily counts of emergency hospital admissions for cardio-respiratory diseases, daily mean air pollution concentrations and weather conditions were collected from January 1998 to December 2007 in Hong Kong. We used generalized additive Poisson model with log link allowing

overdispersion and autocorrelation to examine the differential effects of $PM_{2.5}$ and PM_c. Three parallel time series approaches (bivariate response surface model, joint effect model and parametric stratified model) were used to explore the possible interactions between PM_{10} and gaseous pollutants.

MAIN RESULTS: The associations between PM_c and emergency hospital admissions were statistically significant for respiratory diseases but not for circulatory diseases. In two-pollutant ($PM_{2.5}$ and PM_c) model, an interquartile range increase in the 4-day moving average (lag_{03}) concentrations of PM_c and $PM_{2.5}$ corresponded to 1.05% (95% CI: 0.19%, 1.91%) and 1.81% (95% CI: 0.76%, 2.87%) increase of respiratory admissions, respectively. The effect estimates of $PM_{2.5}$ and PM_c remained robust when adjusting for gaseous pollutants. Meanwhile, an interquartile range increase in lag_{01} concentrations of PM_c and $PM_{2.5}$ was associated with -0.16% (95% CI: -1.07%, 0.76%) and 1.86% (95% CI: 0.85%, 2.88%) change of circulatory admissions, respectively. Some interactions between PM_{10} and gaseous pollutants were found. The effects of PM_{10} on circulatory hospitalizations were greatest during the days when NO_2 or SO_2 concentrations were high (the 3rd tertile, NO_2>64.4 or SO_2>20.9μg/m^3). The effects of PM_{10} on both respiratory and circulatory admissions were greatest during the days when O_3 concentrations were in low to medium levels (<=46.8μg/m^3).

CONCLUSION: We found PM_c to be associated with emergency hospital admissions for respiratory diseases independent of the effect of $PM_{2.5}$, but not for circulatory diseases in Hong Kong. The effects of PM_{10} on cardio-respiratory hospital admissions were modified by gaseous pollutants. There were synergetic interactions between PM_{10} and NO_2 or SO_2 on cardiac hospitalizations and

antagonistic interactions between PM_{10} and ozone on cardio-respiratory hospitalizations. These findings provide supportive evidence for a future PM_c regulation and contribute to the development of a multipollutant air quality management.

Abstract (Chinese)

摘要：

論文題目：	顆粒污染物對人群健康的短期效應---時間序列研究
呈交者：	邱宏
學位：	哲學博士
於香港中文大學 2012 年 6 月	

研究背景：顆粒性空氣污染物（PM_{10}）的危害作用已經爲許多流行病學研究所證實。有學者認爲，空氣動力學直徑小於 2.5 微米的細顆粒（$PM_{2.5}$）和空氣動力學直徑介於 2.5 和 10 微米之間的粗顆粒（PM_c）屬於兩種不同的污染物，應當分別測量。區分粗、細顆粒的健康效應將爲今後分別制訂有關粗、細顆粒的空氣質量標準提供依據。同時，空氣污染物是由顆粒污染物和氣態污染物構成的複雜混合物，二者之間存在一定程度上的聯合或交互作用。

研究目的：以每天心血管系統、呼吸系統疾病急性入院人數爲研究結局，區別估計顆粒污染物 PM_{10} 中粗、細顆粒的健康危害作用，并探討 PM_{10} 與氣態污染物（二氧化氮，NO_2；二氧化硫，SO_2；臭氧，O_3）的交互作用。

研究方法：收集香港 1998 年 1 月至 2007 年 12 月每天心腦血管疾病、呼吸系統疾病急性入院人數，日均污染物濃度，日均氣溫、相對濕度等資料，採用時間序列分析的研究方法，應用 Poisson 廣義相加模型分析顆粒污染物中粗、細顆粒的不同健康效應。同時應用三個平行的時間序列研究模型

（雙變量反應面模型、聯合效應模型和分層模型）探討顆粒污染物和氣態污染物之間潛在的交互作用。

研究結果：研究發現，在校正了 $PM_{2.5}$ 的影響后，PM_c 對呼吸系統疾病導致的急性入院作用顯著，但對心腦血管疾病引起的急性入院則無明顯作用。在雙污染物（PM_c 和 $PM_{2.5}$）模型中，空氣中每一個 IQR（四分位數間距）的 PM_c 和 $PM_{2.5}$ 濃度的增加將使每天急性呼吸系統疾病入院數分別增加 1.05% (95% CI: 0.19%, 1.91%)和 1.81% (95% CI: 0.78%, 2.87%)，使急性心腦血管疾病入院數分別改變 -0.16% (95% CI: -1.07%, 0.76%) 和 1.86% (95% CI: 0.85%, 2.88%)。研究發現某種程 6 度的顆粒污染物和氣態污染物的交互作用。在 NO_2 或 SO_2 高水平（NO_2 濃度高於 64.4μg/m^3 或 SO_2 濃度高於 20.9μg/m^3）的日子里，PM_{10} 對急性心臟疾病入院率的影響高於 NO_2 或 SO_2 低、中水平的日子；而在臭氧高水平（O_3 濃度高於 46.8μg/m^3）的日子里，PM_{10} 對急性呼吸和循環系統疾病入院率的作用低於 O_3 中、低水平的日子。

研究結論：粗、細顆粒污染物對呼吸系統疾病的危害均作用顯著且相對獨立，但對循環系統疾病的危害作用則主要體現於細顆粒污染物。同時，顆粒性污染物的健康危害可能被空氣中的氣態污染物水平所修飾：研究發現 PM_{10} 與 NO_2 或 SO_2 之間的協同作用，以及 PM_{10} 與 O_3 之間的拮抗作用。

List of Contents

List of Tables

List of Figures

List of Abbreviation

APHEA, Air Pollution and Health, a European Approach;

NMMAPS, National Mortality, Morbidity and Air Pollution Study;

RES, diseases of respiratory system;

COPD, chronic obstructive pulmonary disease;

CIR, diseases of circulatory system;

HD, cardiac diseases, heart diseases;

IHD, ischemia heart diseases;

CBD, cerebrovascular diseases;

ICD-9, international statistical classification of diseases, 9^{th} revision;

ERR, excess relative risk;

RR, relative risk;

SI, synergy index;

GAM, generalized additive model;

IQR, inter-quartile range;

lag_{0n}, n-day moving average of current day to previous n days;

PACF, partial autocorrelation function;

TSP, total suspended particles;

PM_{10}, particles with an aerodynamic diameter less than 10 microns;

$PM_{2.5}$, particles with an aerodynamic diameter less than 2.5 microns;

PM_c, particles with an aerodynamic diameter between 2.5 and 10 microns;

NO_2, nitrogen dioxide;

O_3, ozone;

SO_2, sulfur dioxide;

TW, Tsuen Wan.

Acknowledgements

This work was carried out at the School of Public Health and Primary Care in the Chinese University of Hong Kong.

The topic was suggested by Professor Ignatius Tak-sun YU, my supervisor. I would like to express my deepest gratitude and highest admiration to Professor Yu for his efficient guidance and strong support during the whole process of my study. I have benefited enormously from his diligent work and serious attitude in doing the research. At the same time, I would like to express my sincere appreciation to Professor Xiaorong Wang, my co-supervisor, for her helpful advices and kindly concern.

I would also like to extend my sincere thanks to Professor Linwei Tian, Professor Wilson TAM and Professor William Goggins for their help and advices in statistical modeling and data analyses. I am also grateful to Professor Shelly Tse and Professor TW Wong for giving me valuable advices and discussions.

I have been most helped by the warm friendship offered by the academic staff, colleagues and PhD students in the Division of Occupational and Environmental Health. I take this opportunity to thank them together.

Thanks should be sent to Miss. Joyce Leung for her administrative coordination.

This thesis is dedicated to my family for their love and unlimited support!

Chapter 1 Introduction

The association between particulate matter air pollution and cardio-respiratory hospital admissions has been confirmed in many epidemiological studies worldwide over the past two decades (Anderson et al. 2001; Atkinson et al. 2001; Bell et al. 2004; Dockery 2009; Dominici et al. 2006; Ilabaca et al. 1999; Le Tertre et al. 2002; Morris 2001; Norris et al. 1999; Sacks et al. 2011; Slaughter et al. 2005). Most of the studies focused on particles with an aerodynamic diameter less than 10 microns (PM_{10}) or 2.5 microns ($PM_{2.5}$). And it was commonly accepted that the association between PM_{10} and cardio-respiratory diseases might be the result of an underlying association of health effects with fine particles (particles with an aerodynamic diameter less than 2.5 μm, $PM_{2.5}$) (Englert 2004; Levy et al. 2000; Schwartz and Neas 2000). Only in recent years have researchers begun to separately address the health effects of coarse particles (particles with an aerodynamic diameter between 2.5 and 10 microns, PM_c), firstly because PM_c were initially considered as potentially less toxic than fine particles due to their large size and small surface area to mass ratio (Bell et al. 2004; Wilson and Suh 1997), and secondly because of the scarce PM_c measurement data or the simultaneous PM_{10} and $PM_{2.5}$ monitoring data. The large National Mortality, Morbidity and Air Pollution Studies (NMMAPS) conducted in 108 US urban counties failed to find significant effects of PM_c on both respiratory and cardiovascular admissions, but the effects for $PM_{2.5}$ were larger in magnitude and significant (Dominici et al. 2006; Peng et al. 2008). A systematic review of studies on chronic obstructive pulmonary disease, asthma, and respiratory admissions noted that excess relative risks (ERRs) in response to short-term exposure to PM_c were similar to or larger than corresponding estimates for $PM_{2.5}$, and

suggested that PM_c might have adverse effects on the respiratory system (Brunekreef and Forsberg 2005). However, it was less support for a PM_c effect on cardiovascular admissions. Several subsequent studies also reported significant positive associations between PM_c and respiratory hospital admissions but not cardiovascular admissions (Atkinson et al. 2010; Chen et al. 2005; Halonen et al. 2009; Host et al. 2008; Lin et al. 2005; Tecer et al. 2008;).

Most of the previous time series studies on the health effects of air pollution in Hong Kong have focused on PM_{10} due to a lack of $PM_{2.5}$ monitoring data (Wong CM et al. 2001, 2002, 2008a, 2008b; Wong TW et al. 1999, 2002; Wong GWK et al. 2001). A few studies used the limited $PM_{2.5}$ data (Lee et al. 2006; Ko et al. 2007a, 2007b; Wong TW et al. 2006) and no studies considered the effects of PM_c. The criteria pollutants monitored in Hong Kong only include PM_{10} and gaseous pollutants, and the Environmental Protection Department (EPD) is considering $PM_{2.5}$ regulation. Currently a standard specifically for PM_c is not in place or under consideration due to the limited data of independent adverse health effects of PM_c. Additional studies that specifically examine the adverse health effects of PM_c could help in the future to support a PM_c standard. In the first part of this study (Chapter 3), we conducted time series analyses to estimate the differential health effects of $PM_{2.5}$ and PM_c simultaneously on emergency hospital admissions for respiratory and circulatory diseases in Hong Kong, while taking into account for the gaseous pollutants and all time varying confounders. We hypothesized that there were some different effects of $PM_{2.5}$ and PM_c on respiratory and cardiovascular hospitalizations.

Air pollution is a complex mixture of particles and gaseous pollutants to which humans are simultaneously exposed. However, the assessment of health effects of air

pollution has largely focused on the single-pollutant approach aimed at estimating the increasing risk of adverse health outcome associated with the exposure to a single air pollutant, because the criteria pollutants are regulated individually. Besides the particulate matter, the oxidant pollutants (gaseous pollutants including NO_2, O_3 and SO_2) were also identified as very important determinants of health effects in Hong Kong, for both mortality and morbidity from cardio-respiratory diseases (Wong CM et al. 1999, 2001). A previous time series study conducted in Hong Kong reported that a 10 $\mu g/m^3$ increment of current day PM_{10} was associated with about 0.7 and 0.5 percent increase of emergency admissions from respiratory diseases and cardiac diseases, respectively among those aged 65 or above. The corresponding effect sizes for current day NO_2 were 1.3 and 1.2, for lag_1 O_3 were 0.6 and 0.5 respectively (Wong CM et al. 2002).

The effect of a single pollutant identified from single-pollutant approaches was seen as a proxy for another air pollutant or for a mixture of air pollutants (Schlesinger 1995). The scientific community and the US Environmental Protection Agency (EPA) are moving toward a multipollutant approach to quantify the health consequences of air pollution mixture as a whole, which requires an understanding of the joint effects or interaction between pollutants (Dominici et al. 2010).

Only a few epidemiological studies have investigated the interactions between particulate matter and gaseous pollutants. A time series study conducted in Seoul, Korea examined the effects of PM_{10} stratified by the median concentrations of the gaseous pollutants and vice versa, and found that these pollutants were interactive with respect to their effects on the risk of stroke mortality (Hong et al. 2002). Another Hong Kong study detected some significant positive interactions between

NO_2, O_3, and PM_{10} on hospital admissions for cardio-respiratory diseases (Wong TW et al. 1999). A study in Helsinki, Finland observed that O_3 increased the influence of PM_{10}, NO_2, and SO_2 on mortality, especially when O_3 concentration was high (i.e., >42μg/m^3). Interactive effects were also observed between NO_2 and the other pollutants, starting from rather low NO_2 concentration (i.e., 24+ μg/m^3, 10th percentile) (Ponka et al. 1998). Some other researchers reported a harmful interaction at very high concentrations (higher than 200μg/m^3 or 90th percentiles) of PM_{10} and O_3 (Chen et al. 2007; Revich and Shaposhnikov 2010; Tellez-Rojo et al. 2000). On the other hand, two studies reported no interaction between particles and gaseous pollutants on daily mortality (Simpson et al. 1997; Sunyer and Basagana 2001).

The evidence from epidemiological studies in the literature about the interaction between PM_{10} and gaseous pollutants was quite inadequate and inconclusive. The statistical approaches used and power to detect interaction might not be adequate in many previous studies. In the second part of this study (Chapter 4), we used three time series approaches including bivariate response surface model (Roberts 2004), joint effect model (Tse et al. 2011; Wang et al. 2009) and parametric stratified model (Ren et al. 2006, 2008a, 2008b) to examine the joint effects of PM_{10} and gaseous pollutants one by one. We hypothesized there were some possible interactions between PM_{10} and oxidant gases on emergency hospital admissions for cardio-respiratory diseases in Hong Kong.

Chapter 2 Literature Review

2.1. Review on the differential health effects of fine and coarse particles

2.1.1 A brief description of particulate matter air pollution

Particulate matter (PM) refers to the solid or liquid particles suspended in the atmosphere. PM has many sources and can be either primary or secondary in the origin. Primary PM is emitted directly and can be either coarse or fine, whereas secondary PM, which tends to be finer in size, is formed in the atmosphere through physical and chemical conversion of gaseous precursors such as nitrogen oxides (NO_x), sulfur oxides (SO_x), and volatile organic compounds (VOCs). For regulatory and scientific purpose, PM is measured according to the mass concentration within a specific size range (Figure-1 and Table-1).

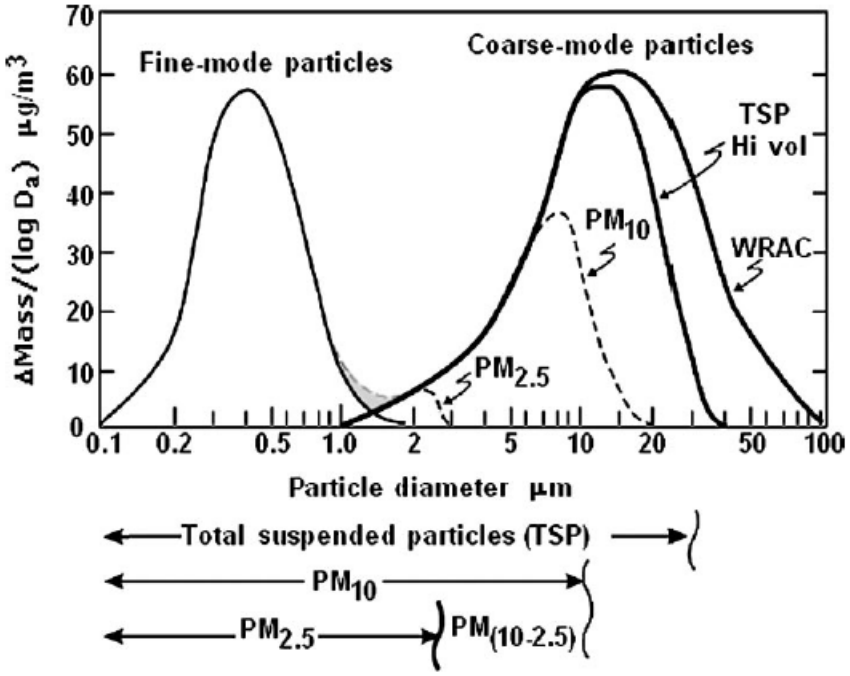

Figure- 1 Size distribution of particulate matter in the air (Wilson and Suh 1997)

Table- 1 Measures of different particle metrics in the air

Particle metric	Definition
Black smoke or British smoke (BS)	A non-gravimetric measure in which air is passed through a filter paper and the darkness of the resulting stain is determined.
Coefficient of haze (COH)	Measure of the intensity of light transmitted through a filter with particles relative to that of a clean filter.
Total suspended particles (TSP)	Particles suspended in the air, with an aerodynamic diameter up to approximately 45 microns.
PM_{10}	Particles with an aerodynamic diameter no larger than 10 microns
Fine, $PM_{2.5}$	Particles with an aerodynamic diameter no larger than 2.5 microns
Coarse, $PM_{10-2.5}$, PM_c	Particles with an aerodynamic diameter between 2.5 and 10 microns
Ultrafine, $PM_{0.1}$	Particles with an aerodynamic diameter no larger than 0.1 microns

Particle size is characterized by aerodynamic diameter, which is the diameter of a uniform sphere of unit density that would attain the same terminal settling velocity as the particle of interest. This measure facilitates size comparison among irregularly shaped particles and refers to the physical behavior of the particles rather than the actual size. Aerodynamic diameter is determined by a particle's shape and density. TSP can be measured by a high volume sampler; however, this method does not collect all particles in the entire coarse mode, as does a wide area aerosol classifier (WRAC) (Figure 1). But in this literature review, coarse particles refers to the particles with an aerodynamic diameter between 2.5 and 10 microns, supposing the particles with an aerodynamic diameter larger than 10 microns would be cleared away quickly in the upper airway and have much less health impact (Lippmann et al. 2000).

Size characteristics are linked to sources and are a determinant of atmospheric transportation, environmental deposition, and the pattern of deposition in the

respiratory system. In typical urban environments, there are two broad sets of source categories: (*a*) combustion sources, including mobile sources (predominantly vehicles) and stationary sources (primarily industrial sources and power plants); and (*b*) mechanical forces, including wind, and vehicle traffic and other activities. The smaller particles result from combustion and stationary sources, whereas the larger particles tend to come from mechanical forces, such as wind or road traffic. In recent health effects research, emphasis has been placed on the smaller particles because they are in the size range that penetrates into the lung without being removed in the upper airway. Fine and coarse particles are separate classes of pollutants and should be measured separately in research and epidemiologic studies (Wilson and Suh 1997).

2.1.2 The objective of this part of literature review

The associations between particulate air pollution and cardio-respiratory mortality or morbidity have been reported in many epidemiological studies over the past 2 decades. Most of the studies focused on PM_{10} or $PM_{2.5}$ (Anderson et al. 2001; Atkinson 2004; Bell et al. 2004; Dominici et al. 2006; Ilabaca et al. 1999; Le Tertre et al. 2002; Lipsett et al. 1997; Morris 2001; Norris et al. 1999; Samet et al. 2000; Schwartz and Neas 2000; Slaughter et al. 2005). It was commonly accepted that the association between PM_{10} and cardio-respiratory diseases may be the result of an underlying association of health effects with fine fraction (Dominici et al. 2006; Levy et al. 2000; Schwartz and Neas 2000). Only in recent years have researchers begun to separately address the health effect of coarse particles (particles with an aerodynamic diameter between 2.5 and 10 μm, PM_c), firstly because PM_c were initially considered as potentially less toxic than fine particles due to their large size and small surface area to mass ratio (Bell et al. 2004; Wilson and Suh 1997) and

secondly because of the scarce PM_c measurement data or the simultaneous PM_{10} and $PM_{2.5}$ monitoring data. The criteria pollutants monitored in Hong Kong only include PM_{10} and gaseous pollutants, and the Environmental Protection Department (EPD) is considering $PM_{2.5}$ regulation. Currently a standard specifically for PM_c is not in place due to the limited data available and not enough evidences from epidemiological studies to support a PM_c standard. The objective of this literature review is to give a comprehensive summary of studies that have investigated $PM_{2.5}$ and PM_c simultaneously and examined the epidemiological evidence for the effects of coarse particles on health.

2.1.3 Methods

2.1.3.1 Inclusion and exclusion criteria of studies/papers

Published epidemiological studies including both time series studies and case cross-over studies that examined the short-term effects of $PM_{2.5}$ and PM_c simultaneously on mortality or morbidity (hospital admissions, emergency department visits, etc.) were traced through Medline and reviewed. Because there was a systematic review published in 2005, which gave a comprehensive summary on the "Epidemiological evidence of effects of coarse airborne particles on health" (Brunekreef and Forsberg 2005) and another review published in 2004 on "Fine particles and human health" (Englert 2004), this present review focused on the studies published after 2004. References of each publication were checked and principal articles were retrieved as well. The emphasis was on comparing effects estimates for fine and coarse particles within studies, so we only included studies giving coefficients for both fractions.

2.1.3.2 Search terms and keywords

While doing the literature search, we used the keywords or terms listed as follows:

(1) Air pollution: *coarse particle* OR *coarse particulate matter* OR *PM(10-2.5)* OR *particle metrics* OR *particle fractions*;

(2) Study design: *time series* OR *case-crossover*;

(3) Health outcome: *mortality* OR *morbidity* OR *hospital admissions* OR *emergency room visits* OR *emergency department visits*.

We also set limits for selection of human studies published in English since January 1, 2004.

2.1.3.3 Information abstracted

For each article meeting the inclusion criteria, we abstracted the information including study location and period, concentrations of $PM_{2.5}$ and PM_c, correlation between $PM_{2.5}$ and PM_c, the main study outcomes, effect estimates for both $PM_{2.5}$ and PM_c, the lag structure, etc. The effects estimates were expressed as relative risk (RR) or excess relative risk (ERR, (RR-1)×100, in percentage change) associated with an interquartile range (IQR) or a 10 μg/m^3 increase of particles concentrations. Effects expressed as percent increase per IQR change of PM is better for the comparison purpose. However, they are always expressed as percent increase per 10 μg/m^3 change of PM in multicity studies, which are not applicable to change to "per IQR change". So we just abstracted the information on effect estimates as those showed in the original articles, but indicated the unit used as "per IQR" or "per 10μg/m^3".

Some studies reported several effect estimates on different health endpoints for both fractions; in this Review one or a few were chosen to be representative of the study, ensuring that the effect estimates for $PM_{2.5}$ and PM_c were from a strictly comparable set of data within the studies. Few studies presented results of analyses in which $PM_{2.5}$ and PM_c were jointly analyzed. The results of two-pollutant models were addressed whenever they were available. Further adjustment by gaseous pollutants or not was also indicated in the tables. We included a column of remarks to indicate the main conclusion of each study.

2.1.4 Results

A total of 21 studies met the inclusion criteria and were included in the final review. Ten of the studies were concerned with identifying the short-term associations between both PM_c and $PM_{2.5}$ with cardio-respiratory mortality (Table-2), while further 13 studies looked at the effects of PM_c and $PM_{2.5}$ on hospital admissions or emergency room visits (Table-3). Two studies used both the mortality and hospital admissions as the health outcomes and were displayed in both Table-2 and Table-3.

2.1.4.1 Short-term effects of $PM_{2.5}$ and PM_c on mortality

The results of time series studies in effects of fine and coarse particles on mortality were summarized in table 2 (Atkinson et al. 2010; Chen et al. 2011; Halonen et al. 2009; Jimenez et al. 2011; Kan et al. 2007; Malig and Ostro 2009; Mallone et al. 2011; Perez et al. 2008, 2009; Zanobetti and Schwartz 2009). The reported correlations between $PM_{2.5}$ and PM_c were typically around 0.5 or less, while the correlations between PM_{10} and PM_c, or $PM_{2.5}$ were much higher, as both PM_c and

$PM_{2.5}$ are parts of PM_{10}. The concentrations of particulate pollutants in Chinese cities were much higher than those in Europe and North America.

There were five studies that not only reported separate estimates for $PM_{2.5}$ and PM_c in single-pollutant model, but also the results of a two-pollutant analysis (Chen et al. 2011; Malig and Ostro 2009; Perez et al. 2008, 2009; Zanobetti and Schwartz 2009). The remained statistically significant effects of PM_c on total and cardiovascular mortality were reported in two of these studies (Malig and Ostro 2009; Perez et al. 2009), while Zanobetti et al. reported the statistically significant effects of PM_c on total and respiratory mortality after adjustment of $PM_{2.5}$ (Zanobetti and Schwartz 2009). Two studies found there were no statistically significant associations between PM_c and daily mortality after adjustment for $PM_{2.5}$, however, the effects of $PM_{2.5}$ remained significant after adjusted for PM_c (Chen et al. 2011; Perez et al. 2008).

Two studies identified the modified effects of Saharan dust on the associations between PM_c and total mortality (Perez et al. 2008) or cardiac mortality (Mallone et al. 2011), which showed the much stronger and statistically significant effect estimates of PM_c during Saharan dust outbreaks. Even in the single-pollutant studies, still some researchers (Halonen et al. 2009; Kan et al. 2007) did not find the significant positive associations between PM_c on mortality, while the significant effects of $PM_{2.5}$ were consistent in the literature. Several studies further adjusted for the gaseous pollutants such as O_3, CO, NO_2 etc. which generally didn't change the effects of $PM_{2.5}$ and PM_c substantially (Atkinson et al. 2010; Halonen et al. 2009; Kan et al. 2007; Mallone et al. 2011; Pererz et al. 2009).

Table- 2 Studies linked PM2.5 and PMc to Daily Mortality

Study	Location and period	Concentration ($\mu g/m^3$/24h)	r	Main outcome	Lags and Unit	RR or ERR% (95%CI) per IQR or 10$\mu g/m^3$ of PM	RR or ERR% (95%CI) from two-pollutant model	Further adjusted by gas	Remarks
Kan HD (Environ Int. 2007)	Shanghai, 2004-2005	*Mean (SD)* $PM_{2.5}$: 56.4 (1.34); PM_c: 52.3 (1.57); PM_{10}: 107.9 (2.39) *Median (IQR)* $PM_{2.5}$: 49.0 (32.5-72.4); PM_c: 42.0 (28.5-66.0); PM_{10}: 93.5 (63.0-135.8)	0.48	79559 TM, 30528 CVD and 8751 RES	Lag_{01}, per 10$\mu g/m^3$	TM: PM_{10}: 0.16% (0.02-0.30%); $PM_{2.5}$: 0.36% (0.11- 0.61%); PM_c: 0.12% (-0.13- 0.36%)	NA	O_3	There is an adverse effect of $PM_{2.5}$ on total mortality and cardio-respiratory mortality. The effect of PM_c was attenuated and less precise.
Perez L (Epidemiology 2008)	in Barcelona, Spain, March 2003-December 2005	*Mean (SD)* PM_c: 15.1 (9.7); $PM_{2.5}$: 24.9 (11.7); *Median (IQR)* PM_c: 12.9 (8.6-19.2); $PM_{2.5}$: 22.4 (17.1-29.9);	0.34	24,850 TM	lag 1; per 10$\mu g/m^3$	TM: PM_c: 2.7% (0.8-4.6%); $PM_{2.5}$: 4.0% (2.3-5.8%);	TM: PM_c: 1.6% (-0.4-3.6%); $PM_{2.5}$: 3.2% (1.5-5.0%); During non-Saharan dust days: PM_c: 1.3% (-0.8-3.4%); $PM_{2.5}$: 3.5% (1.6-5.5%); During Saharan dust days: PM_c: 8.4% (1.5-15.8%); $PM_{2.5}$: 5.0% (0.5-9.7%);	NA	PM_c was much more hazardous during Saharan dust days, while the effect increase was smaller for exposure to $PM_{2.5}$. Differences in chemical composition did not explain these observations. (case-crossover study design)
Malig BJ, (Occup Environ Med. 2009)	15 California counties, 1999-2005	*Mean:* $PM_{2.5}$: 11.1~18.8; *Median (IQR):* PM_c: from 10.6 (6.5, 13.7) to 46.5 (29.8, 52.8) in different counties	-0.03 ~ 0.35	459-29753 TM and 185-12944 CVD.	Lag_2 per 10$\mu g/m^3$	PM_c on TM: 0.7% (-0.1%, 1.5%); CVD: 1.3% (0.1%, 2.5%)	PM_c on TM: 0.8% (0.0%, 1.6%); CVD: 1.3% (0.0%, 2.5%)	NA	Adjustment for $PM_{2.5}$ reduced the precision of the effect estimates of PM_c slightly but had little impact on the magnitude, despite significant associations between $PM_{2.5}$ and mortality. (case-crossover study design)
Halonen JI (Epidemiology 2009)	Helsinki metropolitan area, Finland. 1998-2004	*Median (IQR)*: PM_c: 7.5 (4.9, 12.1); $PM_{2.5}$: 9.5 (5.5, 11.7)	0.25	16,233 CVD and 3,701 RES. (Hospital admissions were also examined.)	Lag_0~lag_3, lag_{05}, per IQR increase	CVD: $PM_{2.5}$ at lag_0: 0.73% (-0.66-2.13%), PM_c at lag_0: -0.01% (-1.52-1.53%) RES: $PM_{2.5}$ at lag_0: 2.67% (-0.39-5.82%); PM_c at lag_1: 2.90% (-0.48-6.39%)	Two-pollutant analysis were only conducted when the pollutants' intercorrelation was <0.7. Results not shown.	CO, NO_2	All particle fractions including Aitken, accumulation, and coarse model had especially adverse respiratory health effects among the elderly. Overall associations were stronger for respiratory than for cardiovascular outcomes.
Zanobetti A (Environ Health Perspect. 2009)	112 US cities for $PM_{2.5}$ and 47 cities for PM_c, 1999-2005	$PM_{2.5}$ median: 5.6-21.5	-	5,609,349 TM, 1,787,078 CVD and 547,660 RES	lag_{01} per 10$\mu g/m^3$	TM: $PM_{2.5}$: 0.98% (0.75-1.22%); PM_c: 0.46% (0.21-0.71%); RES: $PM_{2.5}$: 1.68% (1.04-2.33%); PM_c: 1.16% (0.43-1.89%); CVD: $PM_{2.5}$: 0.85% (0.46-1.24%). PM_c: 0.32% (0.00-0.64%).	TM: $PM_{2.5}$: 0.77% (0.43-1.12%); PM_c: 0.47% (0.21-0.73%); RES: $PM_{2.5}$: 1.63% (0.69-2.59%); PM_c: 1.14% (0.43-1.85%); CVD: $PM_{2.5}$: 0.61% (0.05-1.17%). PM_c: 0.29% (-0.04-0.61%).	NA	The effects were higher in spring. For PM_c, the effects were significant but smaller for all causes analyzed.

Continued

Perez L (Environ Sci Technol. 2009)	in Barcelona, Spain, March 2003-December 2005	*Mean (SD)* PM_c: 14.0 (9.5); $PM_{2.5\text{-}1}$: 5.5 (3.8); PM_1: 20.0 (10.3) *Median (IQR)* PM_c: 12.0 (7.4-18.5); $PM_{2.5\text{-}1}$: 4.4 (2.9-7.4); PM_1: 17.7 (13.2-24.3)	0.45 for $PM_{2.5\text{-}1}$~PM_c, 0.24 for $PM_{2.5\text{-}1}$~PM_1, 0.09 for PM_c~PM_1	4165 RES, 12816 CVD, and 3269 cerebrovascular death	lag 1; per 10μg/m^3	PM_c: CVD: 5.9% (3.1-8.8%); cerebrovascular mortality: 8.6% (3.0-14.5%); RES: 0.2% (-4.5-5.2%)	PM_c in three-pollutant model: CVD: 5.9% (2.6-9.4%); cerebrovascular mortality: 9.8% (3.0-17.1%); RES: -0.2% (-5.7-5.6%)	NO_2, O_3 didn't change the PM_c effects.	Significant positive associations with cardiovascular and cerebrovascular mortality were detected for PM_c at lag_0, lag_1 and lag_{01}, for PM_1 at lag_1. Association with respiratory mortality was only detected for $PM_{2.5\text{-}1}$ at lag 2. (case-crossover study design)
Atkinson RW (Epidemiology 2010)	in central London, north Kensington, 2000-2005	Gravimetric Median (IQR): PM_{10}: 22.0 (17.0, 31.0); $PM_{2.5}$: 15.0 (11.0-22.0); PM_c: 7.0 (5.0-10.0)	0.22	The median numbers for TM, RES and CVD were 145, 22 and 54 per day, respectively. (Hospital admissions were also examined.)	lag_1, per IQR increase	PM_c: TM: 0.96% (0.39-1.48%); CVD: 0.24% (-0.71-1.19%); RES: 2.07% (0.61-3.55%)	Two-pollutant models were conducted as sensitivity analyses, but not for PM_c and $PM_{2.5}$ simultaneously.	PNC (particle number concentrations), NO_3^-, O_3	The results were not consistent across the various outcomes and lags. This study provided some evidences that specific components of the particle mixture for air pollutants may be relevant to specific diseases.
Mallone S (Environ Health Perspect. 2011)	In Rome, Italy, 2001-2004	IQR: 12.8, 10.8, 19.8 for $PM_{2.5}$, PM_c and PM_{10}. Mean (SD): Saharan dust-free days: $PM_{2.5}$: 23.4 (12.5); PM_c: 14.6 (8.7) Saharan dust-affected days: $PM_{2.5}$: 25.6 (9.8); PM_c: 20.7 (12.9)	0.27 and 0.18 for dust-free and dust-affected days	80,423 TM, 33,759 CVD, 24,773 cardiac, 7439 cerebrovascular and 4,574 RES death.	Lag_{02} for TM, and CVD, lag_{05} for RES; per IQR increase	TM: PM_c: 2.96% (1.23-4.72%); PM_{10}: 3.04% (1.53-4.56%); CVD: PM_c: 4.06% (1.50-6.69%); PM_{10}: 2.99% (0.82-5.19%); RES: PM_c: 12.65% (1.18-25.42%). PM_{10}: 4.97% (-2.18-12.63%).	NA	O_3	Significant positive effects of PM_c and PM_{10} on natural and cause-specific mortality were found, with stronger estimated effects on cardiac mortality during Saharan dust outbreaks. Effects of $PM_{2.5}$ for all cause specified mortality were statistically non-significant.
Chen R (Sci Total Environ. 2011)	In three Chinese cities: BeiJing 2007-08; Shanghai 2004-08; ShenYang 2006-08	Mean (SD): Beijing: $PM_{2.5}$: 82 (52); PM_c: 101 (67); Shanghai: $PM_{2.5}$: 55 (30); PM_c: 50 (31); Shenyang: $PM_{2.5}$: 94 (52); PM_c: 49 (30).	0.28 ~ 0.53	TM: 67-119 per day; CVD: 31-54 per day; RES: 7-14 per day.	lag 1; per 10μg/m^3	TM: PM_c: 0.25% (0.08-0.41%); $PM_{2.5}$: 0.32% (0.22-0.43%); CVD: PM_c: 0.25% (0.10-0.39%); $PM_{2.5}$: 0.46% (0.30-0.61%); RES: PM_c: 0.48% (0.20-0.76%). $PM_{2.5}$: 0.50% (0.19-0.81%).	PM_c effects were no longer statistically significant. TM: 0.14% (-0.11-0.39%); CVD: 0.13% (-0.03-0.29%); RES: 0.36% (-0.05-0.77%).	NA	There were no statistically significant associations between PM_c and daily mortality after adjustment for $PM_{2.5}$ in the three Chinese cities. However, the effects of $PM_{2.5}$ remained significant after adjusted for PM_c.
Jimenez E (Int J Environ Health Res. 2011)	In Madrid, Spain			CVD, RES mortality in elderly (>=75)					The results indicated an association between PM_{10} and PM_c and respiratory-specific mortality on the one hand, and between $PM_{2.5}$ and cardiovascular-specific mortality on the other.

TM-total natural cause mortality; CVD-cardiovascular mortality; RES-respiratory mortality.

2.1.4.2 Short-term effects of $PM_{2.5}$ and PM_c on morbidity

Ten papers presenting studies of associations with hospital admissions for respiratory and cardiovascular diseases (Atkinson et al. 2010; Chang et al. 2011; Chen et al. 2004, 2005; Fung et al. 2006; Halonen et al. 2009; Host et al. 2008; Lin et al. 2005; Peng et al. 2008; Tecer et al. 2008) and three studies of emergency room visits (Halonen et al. 2008; Metzger et al. 2004; Slaughter et al. 2005) were identified (Table-3). Three studies conducted in Vancouver, Canada during the same time period (Chen et al. 2004, 2005; Fung et al. 2006) but used the different respiratory endpoints. Authors identified that PM_c and $PM_{2.5}$ had similar effects for COPD hospitalizations in elderly, and the positive associations with overall or repeated respiratory hospital admissions were statistically significant for PM_c but not for $PM_{2.5}$. Another Canadian study conducted in Toronto (Lin et al. 2005) reported the greater effects of PM_c than $PM_{2.5}$ on hospital admissions for respiratory infections in children and the effects of PM_c were independent of gaseous pollutants, while the $PM_{2.5}$ effects were sensitive to the inclusion of the gaseous. Three more studies used asthma or asthma plus COPD as the health endpoints suggested the significant positive effects of both $PM_{2.5}$ and PM_c with asthma hospitalizations in children (Tecer et al. 2008) or with asthma plus COPD hospitalizations in elderly or all ages (Halonen et al. 2008, 2009), but the mechanisms of the respiratory effects of PM_c and $PM_{2.5}$ might differ by age group. Four studies used both respiratory and cardiovascular hospital admissions as the health outcomes (Atkinson et al. 2010; Halonen et al. 2009; Host et al. 2008; Peng et al. 2008), and those conducted in European cities got the similar findings. Researchers from six French cities, Helsinki Finland and central London identified the stronger effects of PM_c than $PM_{2.5}$ on some respiratory morbidity endpoints such as all respiratory diseases in children,

respiratory infection, pneumonia, asthma and COPD hospital admissions. However, $PM_{2.5}$ was found to have stronger effects than PM_c on cardiac admissions and the effects of PM_c on cause-specific cardiovascular hospital admissions were statistically non-significant (Atkinson et al. 2010; Halonen et al. 2009; Host et al. 2008). These three European studies did not fit the two-pollutant models with PM_c and $PM_{2.5}$ jointly which might overestimate the effects of PM_c on respiratory admissions. Another single city study conducted in Atlanta used single-pollutant model did not identify the significant positive associations between PM_c and cardiovascular emergency department visits (Metzger et al. 2004).

Studies in the United States had some different findings with those in European and Canadian cities. The large NMMAPS conducted in 108 US urban counties found significant positive effect of PM_c on cardiovascular admissions in single-pollutant model which lost statistical significance after adjustment for $PM_{2.5}$ in two-pollutant model (Peng et al. 2008). And authors did not find the significant positive effect of PM_c on respiratory admissions as well. PM_c might exhibit higher spatial heterogeneity because of shorter travelling distance and suspending time in the atmosphere, which will also lead to larger exposure measurement error than that of $PM_{2.5}$. So another recent NMMAP study conducted in 59 US counties developed a modeling approach to account for this measurement error and estimated the consistent positive association between PM_c and same-day admissions for cardiovascular diseases, after adjusting for the cofounding effect from $PM_{2.5}$ (Chang et al. 2011).

Table- 3 Studies linked PM2.5 and PMc to Daily Cardio-Respiratory Admissions

Study	Location and period	Concentration ($\mu g/m^3$/24h)	R	Main outcome	Lag and Unit	RR or ERR% (95%CI) per IQR or 10$\mu g/m^3$ of PM	RR or ERR% (95%CI) from two-pollutant model	Further adjusted by gas	Remarks
Metzger KB (Epidemiology, 2004)	in Atlanta, 1993.1.1-2000.8.31	Median (P_{10}, P_{90}) PM_{10}: 26.3 (13.2, 44.7); $PM_{2.5}$: 17.8 (8.9, 32.3); PM_c: 9.1 (4.4, 16.2)	0.43	4,407,535 CVD emergency department visits	Lag_{02} per 10$\mu g/m^3$ for $PM_{2.5}$; per 5$\mu g/m^3$ for PM_c	$PM_{2.5}$: 3.3% (1.0-5.6%); PM_c: 1.2 (-1.5-4.0%)	NA	NO_2, CO or total carbon	CVD visits were associated with $PM_{2.5}$, NO_2, CO, organic carbon and oxygenated hydrocarbons but not with PM_c.
Chen Y (Inhal Toxicol., 2004)	In Vancouver, Canada between June 1995 and March 1999.	Mean (SD): PM_c: 5.6 (3.6); $PM_{2.5}$: 7.7 (3.7) Median (IQR): PM_c: 4.8 (3.1, 7.3); $PM_{2.5}$: 7.0 (5.0, 9.0)	Moderate	4409 COPD hospitalizations in elderly	lag02 per IQR	PM_{10}: 12.8% (5.4-20.8%); $PM_{2.5}$: 7.9 (1.6-14.6%); PM_c: 8.9 (2.5-15.8%).	$PM_{2.5}$: 6.2 (-0.7-13.7%); PM_c: 6.4 (-0.4-13.7%).	COH (coefficient of haze), CO, O_3, NO_2, and SO_2	PM_c and $PM_{2.5}$ has similar effect for COPD hospitalizations. The effects of $PM_{2.5}$ and PM_c were independent of O_3 but became statistically non-significant after adjustment for each other or adjusted by COH, CO, NO_2 or SO_2 one by one.
Slaughter JC (J Expo Anal Environ Epidemiol. 2005)	In Spokane, Washington from Jan. 1995 to Jun. 2001.	90% of concentrations range: PM_{10}: 7.9-41.9; $PM_{2.5}$: 4.2-20.2	0.31	12.2/day for all RES ER visits; 7.3/day for RES HAs; 7.3/day for cardiac HAs.	Lag1-lag3 Per 10$\mu g/m^3$ for $PM_{2.5}$; per 25$\mu g/m^3$ for PM_c.	All RES ER visits: Lag3 $PM_{2.5}$: 1.02 (0.99-1.05); lag3 PM_c: 1.02 (0.99-1.05).	NA	NA	No associations between any size fraction of PM and cardiac or respiratory ER visits or hospital admissions were found. Just a suggestion of greater respiratory effect from $PM_{2.5}$ when compared to PM_c.
LIN M. (Pediatrics 2005)	In Toronto between 1998 and 2001	Mean (SD): $PM_{2.5}$: 9.59 (7.06); PM_c: 10.86 (5.37); Median (IQR): $PM_{2.5}$: 7.5 (4.5-12.3); PM_c: 9.7 (7.0-13.5).	0.33	6782 respiratory infections in Children (age<15)	lag_{03} per IQR change	PM_c: 1.16 (1.07-1.26); $PM_{2.5}$: 1.11 (1.02, 1.22);	NA	CO, SO_2, NO_2 and O_3: PM_c: 1.13 (1.03-1.23); $PM_{2.5}$: 0.94 (0.81, 1.08);	PM_c has larger effect than $PM_{2.5}$ on respiratory infections hospitalizations in children. The effect of PM_c was independent of gaseous, while the effect of $PM_{2.5}$ was sensitive to the inclusion of gaseous pollutants.
Chen Y (Inhal Toxicol, 2005)	In the greater Vancouver area between June 1, 1995, and March 31, 1999.	Mean (SD), IQR: $PM_{2.5}$: 7.7 (3.7), 4.0; PM_c: 5.6 (3.6), 4.2.	0.38	8989 first, 3880 second, and 12,869 overall hospital admissions for RES among the elderly (65+yr)	lag_{02} PM_c per IQR change	PM_c: 1.06 (1.02, 1.09); $PM_{2.5}$: 1.02 (0.98, 1.05)	NA	CO, O_3, NO_2 and SO_2: PM_c: 1.06 (1.02-1.11); $PM_{2.5}$:1.00(0.96, 1.04)	PM_c has a larger effect on overall respiratory admissions than $PM_{2.5}$.
Fung KY (Inhal. Toxicol. 2006)	in Vancouver, Canada, for the period of June 1, 1995, to March 31, 1999	Mean (SD), IQR: $PM_{2.5}$: 7.72 (3.61), 4.00; PM_c: 5.60 (3.88), 4.30.	0.34	14,699 repeated RES readmissions among the elderly (65+yr)	lag_{03}, lag_{05}, lag_{07}; per IQR increase	Lag_{03} PM_c: 1.020 (1.003, 1.037); $PM_{2.5}$: 1.000 (0.982, 1.018)	NA	NA	PM_c was associated with repeated respiratory hospitalizations. Association was not found for $PM_{2.5}$.

Continued

Host S. (Occup Environ Med. 2008)	In six French cities during 2000-2003.	Mean: $PM_{2.5}$: 13.8-18.8; PM_c: 7.0-11.0	0.28 ~ 0.73	RES: 141.6/day; CVD: 209.1/day	Lag01; per 10μg/m^3	RES infection: PM_c: 4.4% (0.9-8.0%); $PM_{2.5}$: 2.5% (0.1-4.8%) RES for age 0-14: PM_c: 6.2% (0.4-12.3%); $PM_{2.5}$: 0.4% (-1.2-2.0%) CVD: PM_c: 0.5% (-1.2-2.3%); $PM_{2.5}$: 0.9% (0.1-1.8%)	NA	NA	PM_c may have a stronger effect than the $PM_{2.5}$ on some morbidity endpoints, especially respiratory diseases. $PM_{2.5}$ may have stronger effect that PM_c on cardiac admissions.
Tecer LH (J Toxicol Environ Health A. 2008)	Zonguldak, Turkey. Dec. 2004-Oct. 2005	Mean: $PM_{2.5}$:29.1; PM_c:24.3; Median (IQR): $PM_{2.5}$: 26.1 (20.8, 34.8); PM_c: 20.8 (13.6, 27.3);	-	2779 Children's (<15yr) hospital admissions include 187 asthma.	Lag_4; per 10μg/m^3 and per IQR	ORs per 10μg/m^3 for asthma: $PM_{2.5}$: 1.25 (1.05-1.50); PM_c: 1.17 (1.05-1.31); PM_{10}: 1.16 (1.06-1.26)	NA	NA	Suggested a greater effect of $PM_{2.5}$ and PM_c on asthma hospital admissions compared with PM_{10} in children.
Halonen JI (Throax 2008)	Helsinki, Finland. 1998-2004	Median (IQR): $PM_{2.5}$: 9.5 (5.5-11.7); PM_c: 9.9 (4.9-12.1)	-	4807asthma(<15yr) ; 6312 and 7239 asthma+COPD hospital emergency room visits among adults and elderly.	Lag0; per IQR increase	For asthm+COPD in elderly: $PM_{2.5}$: 3.09% (0.95-5.27%); PM_c: 2.45% (0.18-4.76%) For asthm+COPD in adults: $PM_{2.5}$: 1.32% (-1.06-3.76%); PM_c: 2.70% (0.21-5.26%)	Two pollutant models conducted for pollutants that were not too highly correlated.	NO_2, CO	Associations between PM_c, $PM_{2.5}$ and asthma+COPD in elderly were found, while in adults, only the association with PM_c was significant. The mechanisms of the respiratory effects of PM_c and $PM_{2.5}$ differed by age group.
Roger D.Peng (JAMA. 2008)	108 US urban counties, 1999-2005	Median (IQR): $PM_{2.5}$: 13.5 (11.1-15.8); PM_c: 9.8 (6.9-15.0)	Median correlation of 0.12	3.7 million CVD and 1.4 million RES	Lag_0, lag_1 and lag_2, per 10μg/m^3	RES: PM_c: 0.33% (-0.21-0.86%); $PM_{2.5}$: 0.44% (0.06-0.82%); CVD: PM_c: 0.36% (0.05-0.68%); $PM_{2.5}$: 0.71% (0.45-0.96%)	PM_c adjusted by$PM_{2.5}$: RES: 0.26% (-0.32%, 0.84%); CVD: 0.25% (-0.11-0.60%)	NA	Unadjusted and adjusted (by $PM_{2.5}$) effects of PM_c were non-statistically significant for CVD or RES admissions.
Halonen JI (Epidemiology, 2009)	Helsinki metropolitan area, Finland. 1998-2004	Median (IQR): PM_c: 7.5 (4.9, 12.1); $PM_{2.5}$: 9.5 (5.5, 11.7)	0.25	10733 pneumonia, 9242 asthma+COPD	Lag_1 for pneumonia, lag_0 for asthma+COPD; per IQR increase	Pneumonia: $PM_{2.5}$: 2.41% (0.64-4.21%), PM_c: 0.55% (-1.34-2.49%) Asthma+COPD: $PM_{2.5}$: 2.48% (0.60-4.39%); PM_c: 2.49% (0.47-4.56)	Two-pollutant analysis were only conducted when the pollutants' intercorrelation was <0.7. Results not shown.	NA	Associations between PM_c, $PM_{2.5}$ and asthma+COPD were found. However, the associations between PM_c, $PM_{2.5}$ and cause-specific cardiovascular admissions were statistically nonsignificant.
Atkinson RW (Epidemiology, 2010)	in central London, north Kensington, 2000-2005	Gravimetric median (IQR): PM_{10}: 22.0 (17.0, 31.0); $PM_{2.5}$: 15.0 (11.0-22.0); PM_c: 7.0 (5.0-10.0)	0.22	Median number: RES: 98/day; CVD: 153/day.	Lag_1 for PM_c, lag_2 for $PM_{2.5}$, Per IQR increase	RES(65+yrs) PM_c: 1.01% (0.10-1.93%); RES(0-14yrs) $PM_{2.5}$: 1.15% (0.22-2.09%);	Two-pollutant models were conducted as sensitivity analyses, but not for PM_c and $PM_{2.5}$ simultaneously.	PNC (particle number concentrations), NO_3^-, O_3	Associations between PM_c, $PM_{2.5}$ and cardiovascular admissions were statistically nonsignificant.
Chang HH; Peng RD (Biostatistics, 2011)	59 US counties, 1999-2005		-0.20~0.59, with median of 0.12	CVD hospital admissions among medicare enrollees	Lag0 per 10μg/m^3	Only used figures to display the effects estimates. Do not have exact values.	PM_c effect adjusted by $PM_{2.5}$: statistically significant.	NA	Consistent positive associations between PM_c, $PM_{2.5}$ and same-day CVD admissions were found.

2.1.4.3 Biological mechanisms underlying the differential effects of $PM_{2.5}$ and PM_c

The biological mechanisms underlying the differential effects of $PM_{2.5}$ and PM_c on cardiovascular emergency hospitalizations might be relevant to the sites of deposition in the respiratory tract and the chemical composition of these two factions. Compared with PM_c, $PM_{2.5}$ has higher number concentration, larger surface area and better lung deposition. PM_c does not penetrate as deeply into the respiratory tract as $PM_{2.5}$ and so more likely to affect the upper and larger airways. $PM_{2.5}$ which is mainly coming from combustion processes has a much greater probability of reaching the small airways and the alveoli of the lung. Particles in the alveolar region are cleaned more slowly than in the conducting airways, which may be one reason for the greater toxic effects of $PM_{2.5}$.

Evidences from toxicological studies showed that on an equal mass basis, $PM_{2.5}$ and PM_c both produce pulmonary inflammation and oxidative stress, which could lead to both respiratory and cardiovascular damage (Pozzi et al. 2003; Shi et al. 2003). A study to examine the different biological activity of $PM_{2.5}$ and PM_c revealed that hemolytic potential was greater for $PM_{2.5}$ than for PM_c in equal mass concentration (Diociaiuti et al. 2001). The biological mechanisms underlying the associations between $PM_{2.5}$ and cardiac diseases also involved modulation of autonomic nervous activity by decreasing heart rate variability (Gold et al. 2000; Magari et al. 2001) and increase of circulating fibrinogen and blood coagulability (Schwartz 2001). Nemmar et al. found that inhaled ultrafine particles could even translate rapidly from the lungs into the blood circulation in humans and thus influence cardiovascular endpoints more directly (Nemmar et al. 2002). An experimental study revealed that exposure of

mice to PM_c resulted in significant pulmonary toxicity while ultrafine PM appeared to enhance cardiac ischemia/reperfusion injury (Tong et al. 2010).

2.1.5 Conclusion remarks

2.1.5.1 Health effects of $PM_{2.5}$ and PM_c on mortality

There are some evidences for the adverse effects of PM_c on mortality. This is most prominent in studies conducted in Barcelona, Spain and Rome, Italy during Saharan dust days when PM_c concentrations are relatively high. PM_c was much more hazardous during Saharan dust days, while the effect increase was smaller for exposure to $PM_{2.5}$.

Only a few studies have analyzed $PM_{2.5}$ and PM_c jointly in two-pollutant model. Study conducted in 112 US cities for $PM_{2.5}$ and 47 cities for PM_c found significant positive associations between PM_c and total mortality, respiratory mortality but not for cardiovascular mortality, while the associations between $PM_{2.5}$ and three mortality endpoints are all statistically significant. Results from studies in Barcelona, Spain got slightly difference. The significant positive associations of PM_c were found for cardiovascular and cerebrovascular mortality but not for respiratory mortality. However, study conducted in three Chinese cities did not find any statistically significant associations between PM_c and total or cardio-respiratory mortality after adjustment for $PM_{2.5}$, while the effects of $PM_{2.5}$ remained significant after adjusted for PM_c.

In conclusion, time series studies relating ambient particulate matter to mortality have in some place provided evidence of an independent effect of PM_c on daily mortality, however, the evidence of association is stronger for $PM_{2.5}$.

2.1.5.2 Health effects of $PM_{2.5}$ and PM_c on morbidity

In studies using COPD in elderly, respiratory infections in children, asthma or asthma plus COPD as the health endpoints, PM_c had stronger or as strong short-term effects as $PM_{2.5}$. And the effects of PM_c were independent of gaseous pollutants, while the $PM_{2.5}$ effects were sensitive to the inclusion of the gaseous. In studies using both respiratory and cardiovascular hospital admissions as the health outcomes, those conducted in European cities (six French cities, Helsinki, Finland and central London) got the similar findings of the stronger effects of PM_c than $PM_{2.5}$ on some respiratory morbidity endpoints such as all respiratory diseases in children, respiratory infection, pneumonia, asthma and COPD hospital admissions. However, $PM_{2.5}$ was found to have stronger effects than PM_c on cardiac admissions. If the spatial heterogeneity and measurement error was considered, the positive association between PM_c and same-day admissions for cardiovascular diseases was also found in 59 US counties, after adjusting for the confounding effect from $PM_{2.5}$.

The body of epidemiological literature on health effects of PM_c and $PM_{2.5}$ is impressive. No single study alone can prove or refute a relationship with one or another fraction. It should be prudent not to neglect any fractions of inhalable particles.

2.2. Review on the joint effects/interactions of particulate matter and gaseous pollutants

2.2.1 Concept of Interaction

In environmental epidemiological research, interaction is thought to be present if the joint effect of the combined pollutants exposure is not equal to the sum of the two or more individual components of the mixture. There are two types of interaction, that is, synergism and antagonism. Synergism is defined as occurring if the effect of the combination is greater than the sum of individual effects, while antagonism is occurred if the effect of the combination is less than the sum of individual effects (Mauderly and Samet 2009). Sometimes synergy is used loosely and considered as the case where none of the mixture components has an effect when given alone, but exposure to the mixture produces some response (Schlesinger 1995). It needs to have evidences on both the individual and the combined effects to evaluate the presence of the interaction.

2.2.2 The objective of this part of literature review

Ambient air pollution is a complex mixture of particles and gaseous pollutants and humans are exposed simultaneously to this pollution mixture. The science communities and US Environmental Protective Agency (EPA) are moving toward a multipollutant approach to quantify the health consequences of air pollution mixture as a whole (Dominici et al. 2010). The objective of this part of literature review is to review and give a comprehensive summary of studies that have investigated the joint effects or interactions between particles and gaseous pollutants.

2.2.3 Methods

2.2.3.1 Search terms and key words

We used the following keywords or terms to do the literature search:

(1) Interaction on pollutants: (*interaction* OR *modif*)* AND *air pollution*;

(2) Study design: *time series* OR *case-crossover*;

(3) Health outcome: *mortality* OR *morbidity* OR *hospital admissions* OR *emergency room visits* OR *emergency department visits*.

2.2.3.2 Information abstract

Among the searched literature, only a small part examined the interaction between particles and gaseous pollutants, while the majority focused on the interaction between pollutant and temperature, season or the effect modification from age, gender and social-economic status. For those studies examined the interaction between pollutants, we abstracted the information including study location and period, main health outcomes used, pollutants considered, methods used to evaluate interaction and the main results on interaction. We also reviewed the methodology used while examining the interaction between pollutant and temperature or season, which was applicable to evaluate the interaction between pollutants. Biological mechanisms relevant to interactive health effects of pollutants were summarized.

2.2.4 Results

2.2.4.1 Studies on the interaction between particulate matter and gaseous pollutants

There were totally 12 studies examined the interaction between particles and gaseous pollutants (Table-4). 4 of them examined the interaction between PM_{10} and NO_2, 8 examined the interaction between PM_{10} and ozone, while 4 concerned about the interaction between PM and SO_2. Another five multicity studies looked at the potential effect modifiers in the second stage meta-regression analysis to explain the observed heterogeneity across different cities (Table-5).

2.2.4.1.1 Studies on the interaction between PM_{10} and NO_2

Only four epidemiological studies examined the interaction between PM_{10} and NO_2 (Hong et al. 2002; Ponka et al. 1998; Sunyer and Basagana 2001; Wong TW et al. 1999). The study conducted in Seoul examined the interaction between particulates and gaseous pollutants on stroke mortality (Hong et al. 2002). Authors reported the ERR for each IQR in NO_2 increased from 2.8% to 3.2% when PM_{10} concentrations were changed from below to above the median level (67.6 $\mu g/m^3$) in the model. At the same time, the ERR for each IQR in PM_{10} decreased from 4.8% to -1.5% when NO_2 concentrations were changed from below to above the median level (59.0 $\mu g/m^3$). Authors drew the conclusion that PM_{10} and gaseous pollutants were interactive with respect to their effects on the risk of stroke mortality**.** However it seems inconsistent about the direction of the interaction in this study. Another study in Helsinki, Finland observed the interactive effects between NO_2 and the other pollutants on cardiovascular mortality, starting from rather low NO_2 concentration

(i.e., 24+ μg/m^3, 10th percentile) (Ponka et al. 1998). A previous Hong Kong study detected some significant positive interactions between NO_2, O_3, and PM_{10} on hospital admissions for cardio-respiratory diseases (Wong TW et al. 1999), however, the positive interactions between PM_{10} and NO_2 were statistically nonsignificant. On the other hand, Sunyer and Basagana reported no interaction between particles and gaseous pollutants on mortality in patients with COPD in Barcelona, Spain (Sunyer and Basagana 2001).

2.2.4.1.2 Studies on the interaction between PM_{10} and O_3

Eight epidemiological studies examined the interaction between PM_{10} and O_3 (Chen et al. 2007; Hong et al. 2002; Ponka et al. 1998; Revich and Shaposhnikov 2010; Simpson et al. 1997; Sunyer and Basagana 2001; Tellez-Rojo et al. 2000; Wong TW et al. 1999). Some researchers reported harmful interaction at high concentrations (higher than 90th or 95th percentiles) of PM_{10} and O_3. A study in Moscow, Russia found on the days with O_3 concentrations above the 90th percentile (41μg/m^3), PM_{10} risk for all-cause mortality was threefold greater and for cerebrovascular disease mortality was fourfold greater (Revich and Shaposhnikov 2010)**.** A study in Shanghai, China found PM_{10} higher than 95th percentile (225.7μg/m^3) would significantly increased the effect of O_3 on total mortality (Chen et al. 2007). Another study in Helsinki, Finland found high concentrations of PM_{10}, ozone, and nitrogen dioxide had a further harmful additive effect on mortality (Ponka et al. 1998). Concentration of O_3 increased the influence of PM_{10}, NO_2, and SO_2, especially when the O_3 concentration was high (i.e., >42μg/m^3, 90th percentile). A study using median as cut-off point found no significant effect of PM_{10} during the days when O_3 levels were below the median (116.7ppb, 228.7μg/m^3), however, a significant effect of

PM_{10} was found on days when O_3 concentrations exceeded the median, which suggested a synergic effect of PM_{10} and O_3 on respiratory mortality on days when ambient O_3 levels are high (Tellez-Rojo et al. 2000). In the above mentioned four studies, three of them chose the 90^{th} or 95^{th} percentiles as cut-off points and two of them detected the interaction between PM_{10} and O_3 at very high concentrations, i.e., PM_{10} higher than 225.7μg/m^3 or O_3 higher than 228.7μg/m^3, which well exceeded the pollution concentration range in Hong Kong and most of the developed countries. In the previous Hong Kong study (Wong TW et al. 1999), authors explored interactions between pollutants using pairwise analyses by entering two pollutants and their interaction term into the model. Each pollutant was analyzed as a continuous variable with the other pollutant as a dichotomous variable using the median as the cutoff point. Significant positive interactions were found for O_3 with high PM_{10} concentrations for respiratory admissions, while for cardiovascular admissions, significant positive interactions were found for both PM_{10} and NO_2 with high O_3 concentrations. The Seoul study (Hong et al. 2002) reported the ERR for an IQR increase of O_3 (32.8μg/m^3) decreased from 5.5% to -2.5% when PM_{10} concentrations were changed from below to above the median level (67.6μg/m^3), while the ERR for an IQR increase of PM_{10} also depended on the different concentrations of gaseous pollutants by increasing from -1.2% to 2.7% when O_3 concentrations were changed from below to above the median level (40.6μg/m^3).

Two studies reported no interaction between PM_{10} and O_3 on mortality (Simpson et al. 1997; Sunyer and Basagana 2001). Sunyer reported no interaction between particles and gaseous pollutants on mortality in patients with COPD in Barcelona, Spain, just based on the statistical non-significance for the product term (both pollutants as continuous variables and all interaction terms had a P-value > 0.5)

(Sunyer and Basagana 2001). Simpson found there was little evidence of interaction between ozone effects and particulates on daily mortality in Brisbane, Australia, using 90th percentiles as the cutoff points (Simpson et al. 1997).

2.2.4.1.3 Studies on the interaction between PM and SO_2

Some studies of Air Pollution and Health: A European Approach (APHEA) followed the procedures identified in APHEA protocol and reported some interactions between particulates and SO_2. A study in Lyon, France found when PM_{13} (particles with an aerodynamic diameter less than 13 microns) concentrations were greater than 60μg/m^3, the joint SO_2 effect on mortality was increased (Zmirou et al. 1996). A study in Athens, Greece observed a stronger effect of SO_2 on daily total mortality when the levels of BS were higher than 100μg/m^3 (Touloumi et al. 1996). A study in Milan, Italy found no significant interaction between TSP and SO_2 on respiratory mortality, while for respiratory hospital admissions, TSP effects were stronger when SO_2 higher than 100μg/m^3 and SO_2 effects were stronger when TSP was higher than 100μg/m^3 (Vigotti et al. 1996). These three European studies suggested some synergy between particulates matter and SO_2 on mortality or hospital admissions. However, another APHEA study conducted in Koln, Germany got the opposite findings. Authors reported that SO_2 effects on daily total mortality were stronger when TSP was below 100μg/m^3 or PM_7 (particles with an aerodynamic diameter less than 7 microns) was below 60μg/m^3. The effects of TSP or PM_7 also tended to be stronger when daily mean SO_2 was below 100μg/m^3, suggesting some antagonism (Spix and Wichmann 1996).

The interaction between PM and SO_2 was only reported in European cities using data almost twenty years ago. During that period from 1975 to 1990, the median value of

SO_2 for several APHEA cities was around 60μg/m^3, which was much higher than that in other developed countries nowadays. This might be the reason that interaction between PM_{10} and SO_2 was not found in other places.

Table- 4 Studies on the Interaction between Pollutants

Study	Location & Period	Main Outcome	Interaction on Pollutants	Methods on Interaction	Results on Interaction
Zmirou D (J Epidemiol Community Health 1996)	Lyon, France, 1985-1990	Four categories of cause of death: total (minus external causes), respiratory, cardiovascular, and digestive causes (as a control condition).	PM_{13} & SO_2	Time series analysis followed the APHEA protocol. An interaction term between SO_2 and binary variable for PM_{13} ($60\mu g/m^3$ as the cutoff) as added to assess the interaction.	When particulates concentrations were greater than $60\mu g/m^3$, the joint SO_2 effect was increased, suggesting some interaction between the two pollution indicators.
Touloumi G (J Epidemiol Community Health 1996)	Athens, Greece, 1975-1987	Daily total mortality	BS & SO_2	Time series analysis followed the APHEA protocol. Effect modification by season as well as among pollutants was tested.	A stronger effect of SO_2 on the daily total mortality was observed when the levels of BS were higher than $100\mu g/m^3$.
Spix C (J Epidemiol Community Health 1996)	Koln, Germany, 1975-1985	Daily total mortality	TSP, PM_7 and SO_2	Time series analysis followed the APHEA protocol.	SO_2 effects were stronger when TSP was below $100\mu g/m^3$ or PM_7 was below $60\mu g/m^3$. Particle effects also tended to be stronger at daily mean SO_2 below $100\mu g/m^3$.
Vigotti MA (J Epidemiol Community Health 1996)	Milan, Italy, 1980-1989	Mortality and Hospital admissions for respiratory diseases	TSP and SO_2	Time series analysis followed the APHEA protocol.	No significant interaction was found between TSP and SO_2 on respiratory mortality. For respiratory hospital admissions, TSP effects were stronger when SO_2 higher than $100\mu g/m^3$ and SO_2 effects were stronger when TSP was higher than $100\mu g/m^3$.
Simpson RW (Arch Environ Health. 1997)	Brisbane, Australia, 1987-1993	mortality	Ozone effects (mainly in summer) and particulates or with sulfur dioxide and nitrogen dioxide.	A general estimating equation analysis, and autoregressive Poisson models were used for daily mortality to examine associations with air pollution variables.	There was little evidence of interaction between the ozone effects (mainly in summer) and particulates or with sulfur dioxide and nitrogen dioxide.
Ponka A (Arch Environ Health. 1998)	Helsinki, Finland, 1987-1993	Mortality form all causes and cardiovascular causes.	PM_{10}, O_3 and NO_2	GAM Poisson regression. Divided pollutants concentrations into three groups ($<P_{10}$, P_{10}-P_{90}, $>P_{90}$) to study pairwise interactions.	Concentration of O_3 increased the influence of PM_{10}, NO_2 and SO_2, especially when O_3 was high ($>42\mu g/m^3$). Interactive effects were also observed between NO_2 and other pollutants, starting from rather low NO_2 (i.e. $24+\mu g/m^3$).

Continued					
Wong TW (Occup Environ Med. 1999)	Hong Kong, 1994-1995	Hospital admissions for respiratory and cardiovascular diseases.	PM_{10}, O_3 and NO_2	Pairwise analyses by entering two pollutants and their interaction term into the model. Each pollutant was analyzed as a continuous variable with the other pollutant as a dichotomous variable using the median as the cutoff point.	For respiratory admissions, significant positive interactions were found for O_3 with high PM_{10} concentrations. For cardiovascular admissions, significant positive interactions were found for both PM_{10} and NO_2 with high O_3 concentrations.
Tellez-Rojo MM (Eur Respir J. 2000)	Mexico City, Jan. 1-Dec. 1, 1994	Daily respiratory mortality	PM_{10} and O_3	Time series analysis. Authors studied the effect of PM_{10}, stratifying for days with high and low O_3 levels (cutoff: median-228.7μg/m^3)	A synergic effect of PM_{10} and O_3 on respiratory mortality on days when ambient O_3 was rather high. No interactive effect between SO_2 and PM_{10} was found.
Sunyer J (Int J Epidemiol. 2001)	Barcelona, Spain, 1990-1995	Death in COPD patients	PM_{10}, O_3, NO_2 and CO	A case-crossover procedure with ambidirectional controls. Interaction between the two pollutants was assessed by including the multiplicative term in the multivariate model.	The association of mortality with PM_{10} was not confounded by the inclusion of gases, while the association of gaseous pollutants was notably reduced after adjustment for particles. There was no interaction between particles and gaseous pollutants (all interaction terms had a P-value >0.5).
Hong YC (Environ Health Perspect. 2002)	Seoul, Korea, 1995-1998	Stroke mortality	PM and gaseous pollutants	GAM Poisson regression. Interactions were determined by the changes of the relative risk of PM_{10} stratified by the level of gaseous pollutants (medians as the cutoff) and vice versa.	These pollutants are interactive with respect to their effects on the risk of stroke mortality.
Chen GH (Biomed Environ Sci. 2007)	Shanghai, China, 2001-2004	Mortality from all non-accidental causes, cardiovascular diseases and respiratory diseases.	PM_{10} and O_3	GAM time series study with stratified analysis, using P_5 and P_{95} as the cut-points for each strata.	Significant interaction was observed only for O_3 in the 95% high PM_{10} strata for total mortality.
Revich B (Air Qual Atmos Health.2010)	Moscow, Russia, 2003-2005	Mortality from all non-accidental causes, ischemic heart diseases and cerebrovascular diseases.	PM_{10} & O_3	Generalized linear bivariate model. Stratified the data for high O_3 level (>P_{90}, 41μg/m^3) and calculated PM_{10} effect than compared it to PM_{10} effect including all days of the study period.	PM_{10}-mortality relationships were significantly modified by O_3 levels. On the days with O_3 concentrations above the P_{90}, PM_{10} risk for all-cause mortality was threefold greater and PM_{10} risk for cerebrovascular disease mortality was fourfold greater than risks estimated including all days.

2.2.4.1.4 Modifiers identified through multicity study

Five multicity studies looked at the potential effect modifiers to explain the observed heterogeneity across different cities (Aga et al. 2003; Atkinson et al. 2001; Gilliland et al. 2001; Katsouyanni et al. 2001; Sunyer et al. 2003) (Table-5). All these studies used the similar statistic approaches, a two-stage time-series model. In the first stage, generalized additive Poisson regression models were fitted in each city. These results were then combined across cities in a second stage meta-regression analysis that looked at potential effect modifiers.

In the studies of Air Pollution and Health: A European Approach 2 (APHEA2), researchers examined the short-term effects of ambient particles on mortality in 29 European cities with emphasis on effect modification (Aga et al. 2003; Katsouyanni et al. 2001). Authors indentified that long term NO_2 concentration as the most important effect modifier: the effects of an increase of 10µg/m^3 in PM_{10} ranges from 0.19% (95% CI = 0.00-0.41%) in cities with low long-term average NO_2 (about 40µg/m^3) to 0.80% (95% CI = 0.67-0.93%) in cities with high long-term average NO_2 (about 70µg/m^3). These studies indicated the possible synergistic interaction between PM_{10} and NO_2 in another way. Besides the long-term average levels of NO_2, temperature, relative humidity, age standardized annual mortality rate and the proportion of the elderly in each city were also identified as modifiers of the effects of PM. The effect size of PM tended to be larger in warmer and drier cities, and in cities with lower age standardized mortality rate or higher proportion of the elderly.

Another APHEA2 study examined the modifiers of the effects of SO_2 on asthma, COPD and all respiratory hospital admissions (Sunyer et al. 2003). Effect

modification among cities by levels of other air pollutants or temperature was not found. This study might have limited power to detect such associations while only seven cities were included. Atkinson et al. investigated the variability of the effect estimates of PM_{10} between eight European cities and identified that annual mean concentrations of ozone in the cities were positively associated with PM_{10} effects on respiratory hospital admissions in the elderly (Atkinson et al. 2001).

A study conducted in 12 southern California communities and examined the effects of ambient air pollution on school absenteeism due to respiratory illness (Gilliland et al. 2001). Authors reported the short-term effects of a 20-ppb change of O_3 on illness-related absenteeism were much greater in communities with lower levels of PM_{10}, compared with those in communities with higher levels (>=35μg/m^3 in annual mean) of PM_{10}. Authors suggested long-term exposure to elevated levels of PM_{10} can affect acute response to O_3 and PM_{10} would act as effect modifier for short-term effect of ozone.

Table- 5 Multicity studies identified the effect modifiers from other pollutant

Study	Location & Period	Main Outcome	Modifiers	Methods	Results on effect Modification
Gilliland FD (Epidemiology 2001)	In 12 southern California communities, 1996.	School absences from respiratory illness.	O_3 and city specific long-term average PM_{10}	A two-stage time-series model: Poisson log-linear model and second stage regression. To assess further whether long-term average pollutant levels modify the acute effects of a pollutant, stratified models were fits using categories of high- and low-pollution communities.	The short-term effects of a 20-ppb change of O_3 on illness-related absenteeism were larger in communities with lower long-term average PM_{10} [223.5% (95% CI = 90.4-449.7)] compared with communities with high average levels [38.1% (95% CI = 8.5-75.8)].
Atkinson RW (Am J Respir Crit Care Med. 2001)	In 8 European cities	Asthma at ages 0-14 years and 15-64 years, COPD, and all respiratory admissions in elderly.	PM10 modified by city characteristics (levels of other pollutants, smoking prevalence, etc.)	Variability in the sizes of the PM_{10} effect estimates between cities was investigated the second stage regression models.	In the 65+ groups PM_{10} estimates were positively associated with annual mean concentrations of ozone in the cities. For asthma admissions (0-14 yr) a number of city-specific factors, including smoking prevalence, explained some of their variability.
Sunyer J (Occup Environ Med. 2003)	In 7 Europena cities for periods of varying duration between 1988 and 1997.	Asthma at ages 0-14 years and 15-64 years, COPD and asthma, and all respiratory admissions at ages 65+ years	SO_2 modified by other pollutants and temperature	In the first stage GAM Poisson regression models were fitted in each city. These results were then combined across cities in a second stage ecological regression that looked at potential effect modifiers.	Effect modification among cities by levels of other air pollutants or temperature was not found.
Katsouyanni K (Epidemiology 2001)	In 29 European cities, 1990-1997	Daily total mortality	PM (PM_{10} and BS) modified by city characteristics (PM_{10}/NO_2, city average NO_2, humidity, etc.)	GAM time series model with second-stage regression models.	In a city with low average NO_2, the estimated increase in daily mortality for an increase of 10μg/m^3 in PM_{10} was 0.19 (95% CI = 0.00-0.41), whereas in a city with high average NO_2 it was 0.80% (95% CI = 0.67-0.93%); The heterogeneity found in the effect parameters among cities reflects real effect modification, which is explained by specific city characteristics.
Aga E (Eur Respir J 2003)	In 28 European cities, 1990-1997	Daily total mortality in the elderly (>=65yrs)	PM (PM_{10} and BS) modified by city characteristics (city average NO_2 level, temperature, humidity, etc.)	A two-stage time-series model: Poisson GAM and second stage meta-regression models to investigate the role of potential effect modifiers in explaining observed heterogeneity.	The effect size of PM was modified by the long-term average levels of NO_2 (higher levels were associated with larger effects) , temperature (larger effects were observed in warmer countries), and by the proportion of the elderly in each city (a larger proportion was associated with higher effects).

2.2.4.2 Methodology used to detect interaction in time series studies

The modeling strategy in time series air pollution studies is to set up a core generalized linear model (GLM) or generalized additive model (GAM) that contains all known time varying confounders (including long term trend, seasonality, temperature, relative humidity, day of week, public holidays, influenza epidemics, autoregressive terms, etc.) to explain the outcome variability, except for pollution exposure, and then add air pollutant concentration linearly to core model to estimate the effects of pollutants on health. Interaction detection is also based on the core model set up. In summary, the following strategies were used to detect interaction between pollutants or pollutant and temperature/season in time series studies.

2.2.4.2.1 Nonparametric bivariable response surface model

The bivariate response surface approach is flexible to examine the interactive effect between two continuous predictors on the dependent variable without a rigid linear assumption and has been used in several air pollution studies (Lipsett et al. 1997; Morris and Naumova 1998; Ren et al. 2006, 2008a, 2008b, 2009; Ren and Tong 2006; Roberts 2004). Local regression smoothing spline (LOESS) was added to GAM core model to display the two-dimensional smooth response surface (Figure-2, 3) controlled by the smooth parameter *span*. It was used to observe the pattern of joint effect graphically. However, it cannot provide the parametric estimates so that it is sometimes difficult to judge whether the effect modification occurs or not.

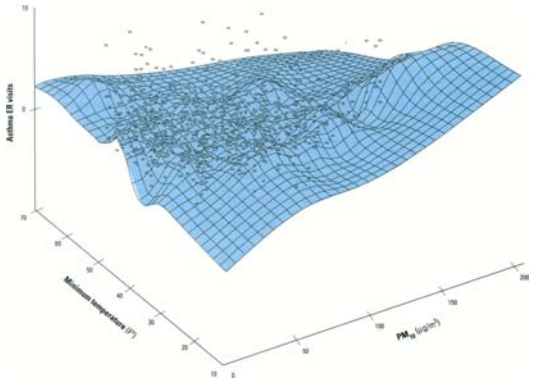

Figure- 2 The joint influence of PM_{10} and minimum temperature on asthma emergency room visits, Santa Clara County, California, in the winters of 1988-1989 through 1991-1992. (Lipsett et al. 1997)

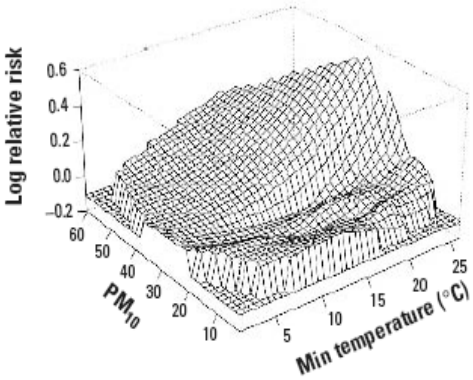

Figure- 3 Bivariate response surfaces of minimum temperature and PM_{10} on health outcomes on current day for cardiovascular mortality in Brisbane, Austria, 1996-2001. (Ren and Tong 2006)

2.2.4.2.2 Non-stratification interaction model

Non-stratification interaction model is fitted by adding the product term of two continuous variables into GAM core model (Sunyer and Basagana 2001). Ren et al. also used this approach as one of the models to detect interaction in their several publications (Ren et al. 2006, 2008a, 2008b, 2009; Ren and Tong 2006). The estimated coefficient of the production term with the significant test shows whether the interaction departed from multiplicative model or not. However, Rothman suggested that interaction as departure from additive model rather than multiplicative model better reflects the biological interaction (Rothman KJ et al. 2008). So interaction detection just based on the inclusion of the product term is not enough.

2.2.4.2.3 Parametric stratified model

Parametric stratified model is fitted by adding the production term of one continuous variable and another categorical variable which is very commonly used in most of the time series studies while detecting interaction. The effect of one pollutant (e.g.

PM_{10}) across the different levels of another variable (e.g. temperature) could be estimated using the following formula. So the modified effect of temperature on PM_{10} could be estimated as well.

$$log(E(Y)) = á + pm_{10} \times factor(temperature\ level) + COVs$$

Where E(Y) is the expected count of health outcome, *COVs* are all time varying confounders identified in the core model. Relative risks (RRs) with confidence intervals were estimated using the method that incorporated coefficient of pollutant and the covariance of pollutant and the interaction term (Figueiras et al. 1998; Lipsett et al. 1997).

2.2.4.2.4 Time series classification and regression tree (CART) model

There was a study which developed time-series CART to explore the possible interactive effects of temperature and air pollution on mortality adjusting for confounders (e.g. seasonality, weekday and autocorrelations at lags of 1 and 2 days) (Hu et al. 2008). The CART is built through a process known as binary recursive partitioning. Given a dataset comprising a response variable and a set of explanatory variables, the algorithm examines every possible binary split on every explanatory variable and chooses the split that optimizes some pre-defined criterion, for example minimizing the sum of the squared deviations from the mean in the resultant two subgroups for continuous data. This splitting or partitioning is then applied to each of the new subgroups. The following Figure-4 depicts a representation of the final CART model, which indicates that the probability of daily death was best decided by an interaction between maximum temperature and SO_2. When maximum temperature was over 32°C (116 days), the expected mortality increased by 7.3% and no further

splits were found to significantly improve the homogeneity of the subgroup outcome (mortality). When daily mean SO_2 exceeded 3.15 parts per billion (ppb, around 8.25μg/m^3) and maximum temperature was in the range of 29°C to 32°C (17 days), the expected mortality rose by 12.1%. However, CART model has not been accepted widely and used to examine interaction in other time series studies.

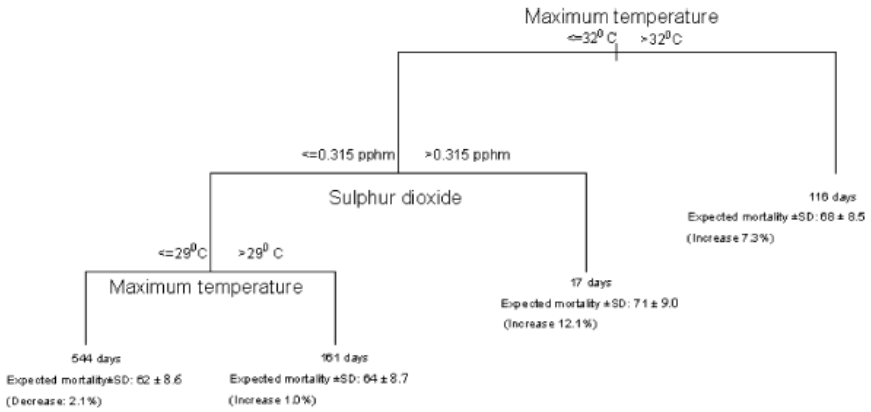

Figure- 4 Regression tree for the relationship between maximum temperature, SO_2 and mortality (Hu et al. 2008)

Expected daily increase rate = (expected mortality-mean of mortality)/mean of mortality.

2.2.4.3 Biological mechanisms of interaction between pollutants

The underlying mechanisms linking air pollutants to increased cardiorespiratory risk have been studied. In general, air pollution exposure is associated with changes in a variety of subclinical physiological end points that relate to cardiorespiratory health, including enhanced pulmonary inflammation and oxidative stress; blood coagulation and thrombosis; vascular dysfunction and atherosclerosis; and impaired cardiac autonomic function (Kampa and Castanas 2008; Pope 2009;). Some researchers even found that the smallest particles could translocate from the lungs into the circulation and thus influence cardiovascular endpoints more directly (Nemmar et al. 2002).

However, the mechanisms underlying specific interaction between particles and gaseous pollutants are not very clear. An early animal study examined the mechanism of physical adsorption hypothesis and suggested the particles served as carriers for nitrogen dioxide, delivering this irritant gas to localized areas within the lungs where the particles deposited (Boren 1964). This was an early example of synergism. A series of experimental studies found the synergistic interaction of ozone and respirable aerosols on rat lungs (Last JA et al. 1986; Warren DL and Last JA 1987; Warren DL et al. 1986, 1988), and the combination of NO_2 with respirable acidic aerosols would also demonstrate interactive effects on rat lungs (Last and Warren 1987).

Mechanisms through the chemical reaction in the exposure atmosphere or on a particle surface, or through the alteration of the pulmonary environment were suggested to explain the interaction between particle and gaseous pollutants (Schlesinger 1995). Combined particles air pollution and ozone exposure increased airway responsiveness in mice (Goldsmith et al. 2002), $PM_{2.5}$ plus ozone impair vascular function and raised diastolic blood pressure (Brook et al. 2009), decreased heart rate variability (HRV) and led to poor cardiac autonomic function (Power et al. 2008). A study examined the interaction between ozone and airborne particulate matter in office air (Molhave et al. 2005) found the combined exposure caused significantly more effects than either ozone exposures or dust exposures, and the effects could be measured as release of cytokines and changes of the respiratory function.

2.2.5 Conclusion remarks

Literature on the examination of interaction between PM_{10} and gaseous pollutants was sparse. Among the 12 studies concerned about this issue, interactive effects of PM_{10} and ozone or NO_2 on cardio-respiratory mortality or hospital admissions were found when pollution concentrations were higher than median or even higher than 90^{th} percentile. Interactive effect between PM_{10} and SO_2 was only found in some European cities in almost twenty years ago whilst the SO_2 concentrations were much higher than those in most of the developed countries nowadays. Several multicity studies identified that the city-specific long-term NO_2 or O_3 levels would be acted as modifiers for the short-term effect of PM_{10} on mortality or morbidity. However, the direction of interaction detected in the studies listed in Table-4 & 5 was inconsistent and inclusive. The reasons for the inconsistent results might be due to the different study population, different pollution composition and concentration range, different end-points examined, and most of all, the inadequate statistical approaches and not enough power to detect interaction.

Chapter 3 Differential health effects of fine and coarse particles

3.1 Objectives

The Specific objectives of this part of study were as follows:

1. To differentiate the health effects of $PM_{2.5}$ and PM_c simultaneously on emergency hospital admissions for respiratory diseases in Hong Kong after adjusting for the gaseous pollutants;

2. To differentiate the health effects of $PM_{2.5}$ and PM_c simultaneously on emergency hospital admissions for cardiovascular diseases in Hong Kong after adjusting for the gaseous pollutants.

3.2 Materials and Methods

3.2.1 Data on particulate pollutants and meteorology variables

Air pollution data between January 2000 and December 2005 were collected from the Environmental Protection Department. There are a total of eleven general monitoring stations in Hong Kong. All of them had PM_{10} and gaseous pollutants (nitrogen dioxide, NO_2; sulfur dioxide, SO_2; ozone, O_3) monitoring, but only three of them (Tsuen Wan, Tap Mun and Tung Chung) had simultaneous $PM_{2.5}$ data during the study period. The Tap Mun and Tung Chung stations are located in remote areas in Hong Kong and the Tsuen Wan station is located geographically close to the center of the entire Hong Kong (Figure-7), and thus the data monitored in Tsuen

Wan station are likely to be more representative of Hong Kong's air quality in general. In addition, the Tsuen Wan station is not in direct proximity to traffic, industrial sources, buildings or residential sources of emissions from the burning of coal, waste, or oil. Therefore, instead of taking the average of the 3 stations with simultaneous PM_{10} and $PM_{2.5}$ data, we used the data from the Tsuen Wan station only.

We calculated twenty-four-hour mean concentrations from non-missing data if at least 18 of 24 hourly concentrations of PM_{10} or $PM_{2.5}$ were available. We used simple average without filling in missing data to compute the daily mean. PM_c concentrations were estimated by subtracting daily mean $PM_{2.5}$ from PM_{10}. Unlike some studies that examined PM_c using every 3rd or 6th day PM data (Lin et al. 2005; Peng et al. 2008), daily data were available during the study period in our study.

We generated daily 24 hour mean concentrations of NO_2, SO_2 and 8 hour mean (10:00~18:00) concentration of O_3 from the same monitoring station Tsuen Wan using the same method as for $PM_{2.5}$. Allowing adjustment for the effect of weather factors on hospital admissions, we collected daily mean temperature and relative humidity for the same period from the Hong Kong Observatory.

3.2.2 Data on emergency hospital admissions for cardio-respiratory diseases

We collected city wide emergency hospital admissions (admissions through the accident and emergency services) for respiratory diseases in Hong Kong from January 2000 to December 2005. The hospitals included for compilation of hospital admissions were the publicly funded hospitals providing 24 hours accident and

emergency services and covering 90% of hospital beds in Hong Kong for local residents (Wong TW et al. 1999). Patient data captured from the computerized medical record system included age, date of admission, source of admission, hospital, residential address and principal diagnosis on discharge coded with *International Statistical Classification of Diseases, 9th Revision* (ICD-9; (WHO 1975)).

We chose the following hospital admissions through the accident and emergency services for diseases as the health outcomes:

- Diseases of the respiratory system (ICD-9:460-519), and its two subsets
  - Chronic obstructive pulmonary diseases (COPD, ICD-9: 490-496);
  - Asthma (ICD-9: 493);
- Diseases of the circulatory system (ICD9:390-459), and its three subsets
  - Cardiac diseases (ICD-9: 390-429);
  - Ischemic heart diseases (IHD, ICD-9: 410-414);
  - Cerebrovascular diseases (ICD-9: 430-438).

We excluded influenza (ICD-9:487.0-487.8) from total respiratory diseases because previous studies demonstrated that influenza outbreak is a potential confounder in the data analysis (Ren et al. 2006). We also compiled emergency hospital admissions for total respiratory and cardiovascular diseases with residential addresses in the region around the Tsuen Wan air monitoring station (including Tsuen Wan, Kwai Tsing and Sham Shui Po districts – designated TW Residents), in order to address the issue of possible exposure misclassification.

3.2.3 Statistical models

3.2.3.1 Core model set up

Generalized additive modeling (GAM) with log link allowing Poisson auto-regression and overdispersion was used to model the relationship between the daily PM_c concentrations and health outcomes (Trevor Hastie 1990). We used penalized smoothing spline (Host et al. 2008; Kan et al. 2007) for filtering out seasonal patterns and long-term trends in daily morbidity, as well as temperature and relative humidity. We also included an adjustment for the day of the week and dichotomous variables including public holidays and influenza epidemics.

To reduce the problems associated with multiple testing and model selection strategies, we followed some previous time series studies to select a *priori* model specification and the degree of freedom (df) for time trend and other meteorological variables (Bell et al. 2008; Lee et al. 2006; Peng et al. 2008; Wong CM et al. 2002). Specifically, we used a *df* of 7 per year for time trend, a *df* of 6 for mean temperature of current day ($Temp_0$) and the moving average of previous 3 days ($Temp_{1-3}$), and a *df* of 3 for relative humidity on current day ($Humidity_0$). A somewhat larger value of degree of freedom was necessary for temperature in order to capture the well-known "J-shape" nonlinear relationship between temperature and morbidity. We included the day of the week (*DOW*) and public holidays (*Holiday*) in the model as dummy variables (Schwartz et al. 1996). To adjust for the confounding effect of influenza epidemics on emergency hospital admissions, we entered a dummy variable for the weeks with the number of influenza hospital admissions exceeding the 75 percentile in a year into the core model (Wong CM et al. 2002).

Briefly, we set up a core model to remove the long term trends, seasonal variations and adjust for time varying confounders as follows:

$$log(E(Y)) = \alpha + s(t, df=7/year) + s(Temp_0, df=6) + s(Temp_{1-3}, df=6) + s(Humidity_0, df=3) + \beta_1 * DOW + \beta_2 * Holiday + \beta_3 * influenza \quad \ldots\ldots [1]$$

Here *E(Y)* means the expected daily emergency hospital admission counts on day t; *s(.)* is the smoother based on penalized spline method; β is the regression coefficient.

In an attempt to minimize autocorrelation, which would bias the standard errors, we specified that the absolute values of PACF for the residuals of core model had be less than 0.1 for the first 2 lag days (Wong CM et al. 2008b). If these criteria were not met, we then added autoregressive terms such as lag_1 to lag_n of outcome variables to model [1] to reduce autocorrelation. As an example, we set up the final core model to fit emergency hospital admissions for total respiratory diseases. Figure-5 is the residual plot and the PACF of residuals of the core model [1]. The absolute values of PACF for the residuals of core model were larger than 0.1 for the first 3 lag days, which showed some autocorrelations in the residuals. So we included three autoregressive terms ($lag_1 \sim lag_3$ of outcome variable) to core model and then the PACF for residuals of the final core model showed no more autocorrelations (Figure-6).

The final core model to fit emergency respiratory hospitalizations is as follows:

$$log(E(RES)) = \alpha + s(t, df=7/year) + s(Temp_0, df=6) + s(Temp_{1-3}, df=6) + s(Humidity_0, df=3) + \beta_1 * DOW + \beta_2 * Holiday + \beta_3 * influenza + RES_1 + RES_2 + RES_3 \quad \ldots\ldots [2]$$

Here *E(RES)* means the expected daily emergency respiratory hospitalizations counts on day t; RES_n means lag n day's emergency respiratory hospitalizations counts.

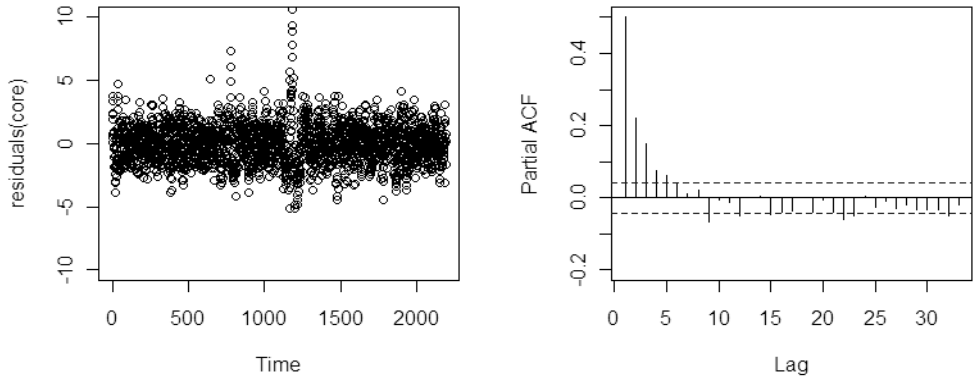

Figure- 5 Residual and the PACF of residuals of the core model [1]

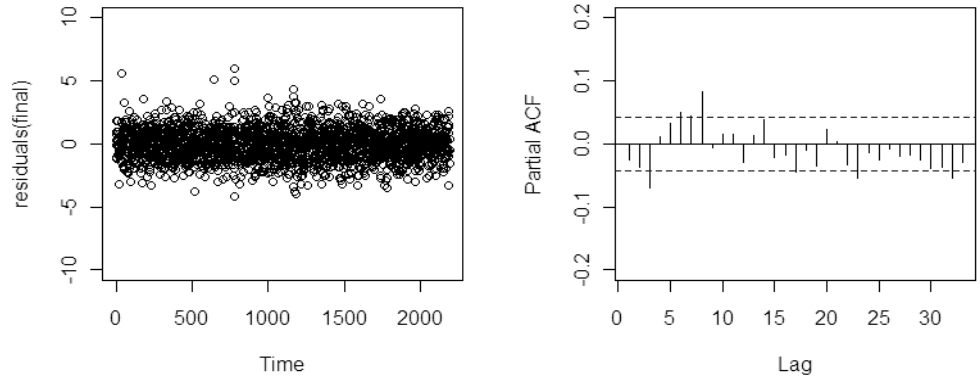

Figure- 6 Residual and the PACF of residuals of the final core model [2]

3.2.3.2 Single-pollutant and two-pollutant models

If there were no discernible patterns and no autocorrelation in the residuals, potential confounding was considered not evident in the daily variations of health outcomes. We then estimated the linear effect of PM pollutant with different lag structures including both single-day lag (current day up to previous 5 days: lag_0-lag_5) and multi-day lag (average of current day and the previous 1-3 days: lag_{01}, lag_{02} and

lag_{03}), which were so-called single-pollutant models. We also put $PM_{2.5}$ and PM_c at the same lag into model simultaneously to estimate the effect of $PM_{2.5}$ adjusted for PM_c or the effect of PM_c adjusted for $PM_{2.5}$, which was so-called two-pollutant model. In the two-pollutant models, concentration-response relationship estimation and sensitivity analyses, we focused on the biologically plausible effects of PM and chose 4-day average exposure (lag_{03}) for respiratory and 2-day average exposure (lag_{01}) for cardiovascular hospitalizations (Anderson et al. 2001; Chen et al. 2004; Host et al. 2008).

3.2.3.3 Concentration-response relationship

In order to justify the assumption of linearity between the logarithm of emergency hospital admissions and particulate concentrations, we used smoothing function to graphically examine the concentration-response relationships between cardio-respiratory hospital admissions and $PM_{2.5}$, PM_c respectively (Kan et al. 2007; Wong CM et al. 2002). The formulas are as follows, using the respiratory endpoint as an example.

$$log(E(RES)) = \alpha + s(PM_{2.5}, df=3) + s(t, df=7/year) + s(Temp_0, df=6) + s(Temp_{1-3}, df=6) + s(Humidity_0, df=3) + \beta_1 * DOW + \beta_2 * Holiday + \beta_3 * influenza + RES_1 + RES_2 + RES_3 \quad \ldots\ldots [3]$$

$$log(E(RES)) = \alpha + s(PM_c, df=3) + s(t, df=7/year) + s(Temp_0, df=6) + s(Temp_{1-3}, df=6) + s(Humidity_0, df=3) + \beta_1 * DOW + \beta_2 * Holiday + \beta_3 * influenza + RES_1 + RES_2 + RES_3 \quad \ldots\ldots [4]$$

3.2.3.4 Sensitivity analysis

In addition to data analysis with the entire range of particulate concentrations, we performed sensitivity analysis excluding days with extremely high or low concentrations (i.e. the highest 1% and lowest 1% values were excluded).

Given that it was not easy to determine the optimal values of *df* for time trend and weather conditions in GAMs, whether from statistical or biological plausibility perspectives, we did sensitivity analysis to examine the impact of df selection on the effect estimates of PM_c or $PM_{2.5}$.

In order to address possible exposure misclassification while using pollution data from one central monitoring station, we did sensitivity analysis by restricting the emergency hospital admissions for total respiratory and cardiovascular diseases to persons residing in Tsuen Wan region (TW Residents). We also examined the effects of $PM_{2.5}$ and PM_c on emergency cardio-respiratory hospitalizations after adjusting for the confounding effects of gaseous pollutants (NO_2, SO_2 and O_3).

We conducted all analyses in R2.10.0 while loading MGCV package (R Development Core Team, 2010). We reported the results as the percent increase (Excess relative risk, ERR, %) with 95% confidence interval (CI) in daily emergency hospital admissions for an inter-quartile range (IQR) increment of PM concentration.

3.3 Results

3.3.1 Location of Tsuen Wan station, Tsuen Wan region

Figure-7 is a map of Hong Kong, showing the location of Tsuen Wan monitoring station, Tsuen Wan region where we conducted the restricted analysis in Tsuen Wan residents, and the locations of other general monitoring stations.

Figure- 7 Location of Tsuen Wan station, Tsuen Wan region (central dark-grey area) and all the other general monitoring stations in Hong Kong

3.3.2 Air pollution concentrations and meteorological factors

During the study period between 1 January, 2000 and 31 December, 2005, there were 195 days with missing PM_c data, which accounted for 8.9% of the total number of

days. The daily mean concentrations of $PM_{2.5}$ and PM_c were 39.4 and 16.6 μg/m^3, with an IQR 26.3 and 10.9 μg/m^3 respectively. $PM_{2.5}$ accounted for a substantial part of the mass concentration of PM_{10} in Hong Kong: the ratio of $PM_{2.5}$ to PM_{10} ranged from 40% to 98%, with an average of 70%. In other words, PM_c accounted for about 30% of PM_{10} mass concentration. The daily mean concentrations of NO_2, SO_2 and O_3 were 64.4, 22.9 and 31.1 μg/m^3, respectively (Table-6). Generally, PM_{10} was strongly correlated with both $PM_{2.5}$ (correlation coefficient, r=0.97) and PM_c (r=0.84); $PM_{2.5}$ and PM_c were moderately correlated (r=0.68). The correlation coefficients for $PM_{2.5}$ and gaseous pollutants were moderate to high (r=0.79 for NO_2, r=0.46 for SO_2, r=0.47 for O_3), while the correlation coefficients for PM_c and gaseous pollutants were low to moderate (r=0.56 for NO_2, r=0.27 for SO_2, r=0.37 for O_3) (Table-7).

Table- 6 Distribution of air pollution concentrations in Tsuen Wan and weather conditions in Hong Kong from 2000 to 2005

Variables	No. of days	Mean	SD	Percentiles				
				Min.	25th	50th	75th	Max.
Pollution concentration ($\mu g/m^3$)								
PM_{10}	1998	56.1	27.8	13.5	34.9	49.2	72.5	231.5
$PM_{2.5}$	1997	39.4	20.7	8.9	23.8	34.8	50.1	179.8
PM_c	1997	16.6	9.2	0.8	10.0	14.5	20.9	82.9
NO_2	1995	64.4	22.4	13.0	48.4	61.6	77.4	193.9
SO_2	1998	22.9	17.1	1.0	11.3	18.3	28.7	143.3
O_3	1995	31.1	24.3	1.0	13.2	24.2	42.8	171.7
Meteorology measures								
Temperature (^oC)	2192	23.5	5.0	8.2	19.6	24.9	27.8	31.8
Relative humidity (%)	2192	78.2	9.7	32	73	79	85	97

Abbreviations: SD-standard deviation; Min.-minimum; Max.-maximum.

Table- 7 Pearson Correlation coefficients between particles concentration, gaseous pollutants and weather conditions*

Pollutants	PM_{10}	$PM_{2.5}$	PM_c	NO_2	SO_2	O_3	Temperature
PM_{10}	1.000						
$PM_{2.5}$	0.969	1.000					
PM_c	0.836	0.675	1.000				
NO_2	0.771	0.786	0.560	1.000			
SO_2	0.432	0.461	0.267	0.493	1.000		
O_3	0.475	0.472	0.370	0.303	0.022	1.000	
Temperature	-0.304	-0.285	-0.278	-0.298	0.163	0.054	1.000
Relative humidity	-0.470	-0.409	-0.498	-0.282	-0.062	-0.582	0.213

*: All correlation coefficients except that between O_3 and SO_2 are statistically significant ($P<0.05$).

3.3.3 Emergency hospital admissions for cardio-respiratory diseases

From January 1, 2000 to December 31, 2005, we recorded a total of 710,247 hospital admissions for respiratory diseases and 612,551 hospital admissions for circulatory diseases in the study population. Among them the hospitalizations through accident and emergency services (emergency hospital admissions) were 518,864 for respiratory and 338,123 for cardiovascular diseases, respectively. On average, there were 237, 81 and 20 emergency hospital admissions per day for total respiratory diseases, COPD and asthma respectively. And there were 154, 95, 30 and 47 emergency hospital admissions per day for total circulatory diseases, cardiac diseases, IHD and cerebrovascular diseases respectively. The average numbers of emergency hospital admissions in Tsuen Wan residents were about 50 per day for respiratory diseases and 32 per day for circulatory diseases (Table-8).

Table- 8 Summarized statistics of daily emergency hospital admissions for cardio-respiratory diseases in Hong Kong from 2000 to 2005 (n=2192)

			Percentiles				
Variables	**Mean**	**SD**	**Min.**	**25th**	**50th**	**75th**	**Max.**
Daily emergency hospital admissions for respiratory diseases							
Total Respiratory Diseases	236.7	55.4	89	198	230	269	518
COPD	81.1	20.3	22	68	80	95	165
Asthma	19.6	8.0	1	14	19	25	61
Respiratory Diseases in TW residents	50.0	12.4	18	41	49	57	104
Daily emergency hospital admissions for cardiovascular diseases							
Total circulatory diseases	154.3	24.3	66	139	153	169	243
Cardiac diseases	95.1	18.6	34	82	94	106	165
Ischemic heart diseases	30.1	6.8	10	25	30	34	64
Cerebrovascular diseases	46.7	7.9	22	41	46	52	79
Total circulatory diseases restricted to TW residents	32.3	7.5	12	27	32	37	61

Abbreviations: TW-Tsuen Wan; SD-standard deviation; Min.-minimum; Max.-maximum.

3.3.4 Regression results and Sensitivity analysis

3.3.4.1 Effects of Coarse Particulate Matter on Emergency Hospital Admissions for Respiratory Diseases

Figure-8 summarizes the effects of PM_c on emergency hospital admissions for respiratory diseases, COPD and asthma. We found that PM_c was significantly associated with emergency hospital admissions for total respiratory diseases and COPD on nearly all the lags examined in single pollutant models, while the associations with asthma hospitalizations were positive, but with statistically significant only for lag_4, lag_5 and lag_{03} (Figure-8).

An IQR increase in the 4-day moving average concentration of PM_c (lag_{03}) corresponded to 1.94% (95% CI: 1.24%, 2.64%), 3.37% (2.26%, 4.49%) and 2.32% (0.14%, 4.55%) increase of emergency hospital admissions for total respiratory diseases, COPD and asthma, respectively. After adjusting for $PM_{2.5}$ in the two-pollutant models, the effects of PM_c on respiratory and COPD hospital admissions were attenuated, but remained statistically significant with an ERR of 1.05% (95%CI: 0.19%, 1.91%) and 1.78% (0.41%, 3.16%) respectively , while the effect of PM_c on asthma hospitalizations became statistically insignificant (Table-9).

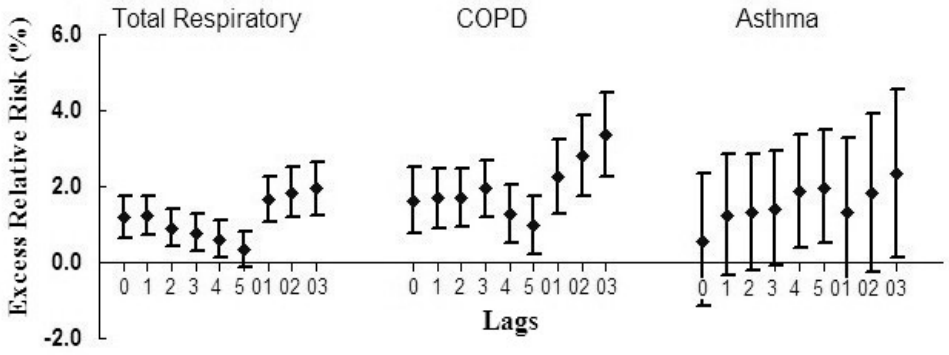

Figure- 8 Percent increase (ERR % with 95%CI) in emergency hospital admissions due to total respiratory diseases, COPD and asthma for an IQR (10.9-µg/m^3) increase in PM_c concentrations with different lag days (lag_0~lag_5, lag_{01}~lag_{03})

Table- 9 Percent increase (ERR% with 95%CI) of emergency respiratory hospital admissions associated with an IQR increase in particle concentrations*

Pollutant	Total Respiratory	COPD	Asthma
Single Pollutant Model			
PM_c	1.94 (1.24, 2.64)	3.37 (2.26, 4.49)	2.32 (0.14, 4.55)
$PM_{2.5}$	2.58 (1.73, 3.44)	4.44 (3.11, 5.80)	4.35 (1.66, 7.11)
Two Pollutants Model			
PM_c	1.05 (0.19, 1.91)	1.78 (0.41, 3.16)	0.27 (-2.42, 3.03)
$PM_{2.5}$	1.81 (0.76, 2.87)	3.13 (1.48, 4.81)	4.14 (0.77, 7.63)

*Four-day moving average (current day to previous 3 days, lag_{03}) of particle concentrations were used to estimate the health effects. IQR: interquartile range, for PM_c and $PM_{2.5}$ was 10.9 and 26.3µg/m^3 respectively.

Figure-9 shows the smoothing curves of the concentration-response relationships between PM_c and emergency hospital admissions for total respiratory diseases. The concentration-response curve tended to become nonlinear at the higher concentrations of PM_c, but uncertainty was high due to the data paucity at this range (Figure-9A). Considering the linear assumption in estimating the PM_c effect in GAM, we then excluded the highest 1% and the lowest 1% extremes of PM_c concentrations. The curve appeared essentially linear after excluding the 2% extremes of PM_c concentrations (Figure-9B). The estimated effect (slope) of PM_c modeled as a linear variable after excluding days with extreme concentrations increased slightly and remained statistically significant, either before or after adjustment for $PM_{2.5}$ (Table-10).

Sensitivity analysis restricting to emergency respiratory hospitalizations in Tsuen Wan residents showed that the risk estimates of PM_c were slightly higher with wider confidence intervals, but remained statistically significant after adjustment for $PM_{2.5}$. Adjustment for the gaseous pollutants showed that the effects of PM_c on total respiratory hospitalizations were stable and not sensitive to the inclusion of NO_2, SO_2 or O_3 into the model (Table-10).

Figure-10 displays the percent increase of emergency respiratory hospital admissions associated with an IQR (10.9 $\mu g/m^3$) increase in 4-day moving average concentration of PM_c (lag_{03}), with a range of different *df* choices for the smoother of time, temperature and relative humidity in single pollutant model. Varying the *df* for time trend (within the range of 6-12 per year) and for weather conditions (within the range of 3-12) did not affect the regression results substantially, suggesting that the effect

estimates for PM_c based on a *df* of 7 per year for time trend, a *df* of 6 for temperature and 3 for relative humidity were relatively robust in this respect.

Table- 10 Percent increase (ERR% with 95%CI) of emergency hospital admissions for total respiratory diseases associated with an IQR increase in particle concentrations*

	Restrict analysis for PM_c in P_1~P_{99} [a]	Restrict analysis in TW residents [b]	Additionally adjusted for gaseous pollutants [c]		
			NO_2	SO_2	O_3
Single pollutant model					
PM_c	2.37 (1.51, 3.24)	2.66 (1.33, 4.02)	1.58 (0.86, 2.30)	1.96 (1.26, 2.67)	1.85 (1.15, 2.56)
$PM_{2.5}$	2.55 (1.67, 3.43)	3.02 (1.42, 4.65)	1.98 (1.04, 2.94)	2.74 (1.87, 3.63)	2.43 (1.55, 3.32)
Two pollutants model					
PM_c	1.32 (0.23, 2.42)	1.78 (0.11, 3.47)	1.07 (0.21, 1.94)	1.02 (0.16, 1.89)	1.08 (0.22, 1.95)
$PM_{2.5}$	1.70 (0.59, 2.82)	1.72 (-0.26, 3.74)	1.19 (0.05, 2.33)	1.97 (0.89, 3.06)	1.62 (0.53, 2.71)

*: Four-day moving average (current day to previous 3 days, lag_{03}) of particle concentrations were used to estimate the health effects. IQR: interquartile range, for PM_c and $PM_{2.5}$ was 10.9 and 26.3μg/m^3 respectively. [a:] Analysis restricted to 1% to 99% percentiles (6.42-42.96 μg/m^3) of PM_c concentration; [b]: Analysis restricted to hospital admissions in Tsuen Wan residents; [c]: Analysis covered the entire range of PM_c concentration and city-wide respiratory admissions.

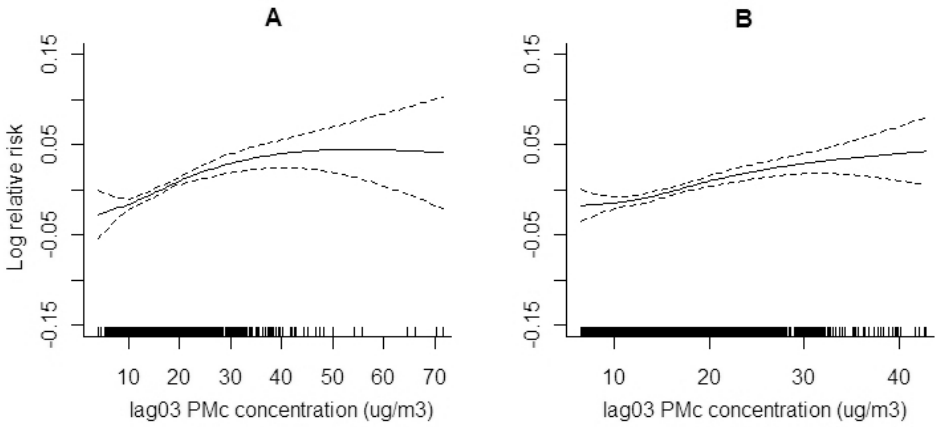

Figure- 9 Concentration-response curves between the logarithm of emergency respiratory hospital admission and particle concentration (df=3)

The density of the vertical bars on the x-axis shows the distribution of pollutant concentration. A: analysis covering the entire range of PM_c concentrations; B: restricted analysis excluding days with the lowest 1% and the highest 1% PM_c concentrations.

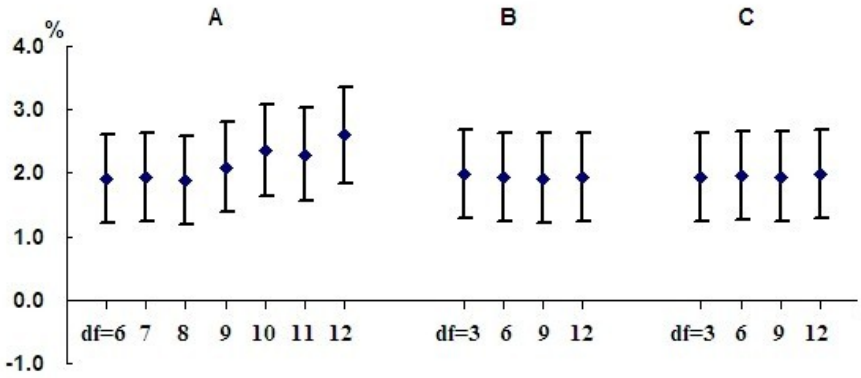

Figure- 10 Sensitivity analyses for varying df for time trend and weather conditions on emergency respiratory hospital admissions based on an IQR increase of lag_{03} PM_c concentrations.

A: df=6~12 per year for time trend; B: df=3~12 for current day and previous 3 days' mean temperature; C: df=3~12 for current day relative humidity.

3.3.4.2 Differential effects of fine and coarse particles on emergency hospital admissions for cardiovascular diseases

Figure-11 summarizes the effects of $PM_{2.5}$ (Figure-11A) and PM_c (Figure-11B) on emergency hospital admissions for total circulatory diseases, cardiac diseases, IHD and cerebrovascular diseases. We found both $PM_{2.5}$ and PM_c to be significantly associated with total circulatory, cardiac and especially IHD emergency hospital admissions on nearly all the lags examined in the single pollutant models, but not with cerebrovascular diseases. An IQR increase in lag_{01} concentration of $PM_{2.5}$ corresponded to 1.75% (95% CI: 0.94%, 2.57%), 2.61% (1.60%, 3.64%) and 3.47% (1.84%, 5.12%) increase of emergency hospital admissions for total circulatory diseases, cardiac diseases and IHD respectively. The corresponding effect estimates of PM_c in lag_{01} were a little lower, with an ERR of 0.83% (95% CI: 0.10%, 1.58%), 1.49% (0.57%, 2.41%) and 2.40% (0.90%, 3.92%) increase of emergency hospital admissions for total circulatory diseases, cardiac diseases and IHD respectively (Table-11).

In the two-pollutant models, the effects of $PM_{2.5}$ on emergency hospital admissions for total circulatory, cardiac and IHD changed slightly and remained statistical significant with an ERR of 1.86% (95%CI: 0.85%, 2.88%), 2.50% (95%CI: 1.25%, 3.77%) and 2.97% (0.96%, 5.02%) respectively. However, the effects of PM_c attenuated greatly and lost statistically significant. We did not find any effects of PM_c on each subset of circulatory hospitalizations independent of $PM_{2.5}$ (Table-11).

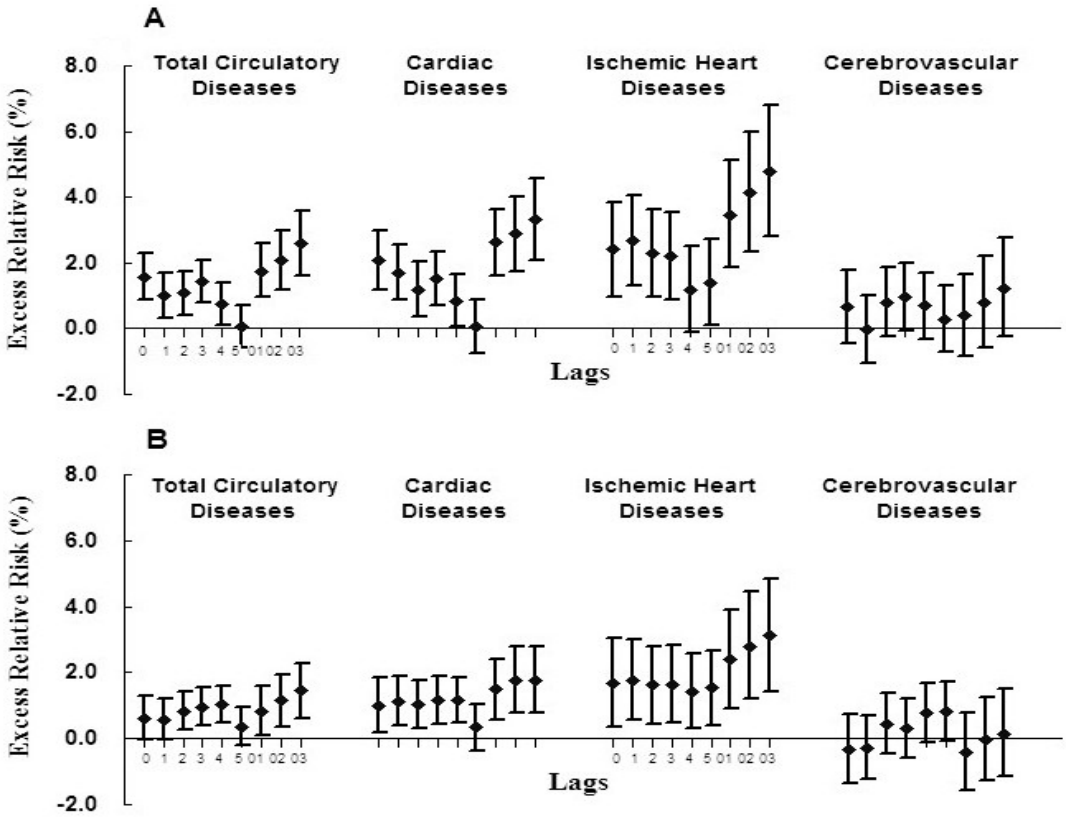

Figure- 11 Percent increase (ERR % with 95%CI) in emergency hospital admissions for circulatory diseases for an IQR increase in $PM_{2.5}$ (26.3-μg/m^3) (A) and PM_c (10.9-μg/m^3) (B) concentrations with different lag structures (lag_0~lag_5, lag_{01}~lag_{03}) in single pollutant model.

Table- 11 Percent increase (ERR% with 95%CI) of emergency circulatory hospital admissions associated with an IQR increase in particle concentrations*

Pollutant	Diseases of Circulatory System	Cardiac Diseases	Ischemic Heart Diseases	Cerebrovascular Diseases
Single Pollutant Model				
$PM_{2.5}$	1.75 (0.94, 2.57)	2.61 (1.60, 3.64)	3.47 (1.84, 5.12)	0.39 (-0.85, 1.65)
PM_c	0.83 (0.10, 1.58)	1.49 (0.57, 2.41)	2.40 (0.90, 3.92)	-0.41 (-1.57, 0.77)
Two Pollutants Model				
$PM_{2.5}$	1.86 (0.85, 2.88)	2.50 (1.25, 3.77)	2.97 (0.96, 5.02)	1.01 (-0.54, 2.59)
PM_c	-0.16 (-1.07, 0.76)	0.17 (-0.95, 1.29)	0.76 (-1.07, 2.63)	-0.97 (-2.41, 0.49)

* Average concentration of current day and previous 1 day (lag_{01}) of particle concentrations were used to estimate the health effect. IQR: interquartile range, for PM_c and $PM_{2.5}$ was 10.9 and 26.3μg/m^3 respectively.

Figure-12 shows the smoothing curves of the concentration-response relationships between $PM_{2.5}$, PM_c and emergency hospital admissions for total circulatory diseases. The concentration-response curves for $PM_{2.5}$ and PM_c tended to become nonlinear at the higher concentration which was probably due to the data paucity at this range (Figure-12A). Considering the linear assumption in estimating the particles effect in GAM, we then excluded days with the highest 1% and the lowest 1% extremes of $PM_{2.5}$ and PM_c concentrations. The curves appeared essentially linear after that (Figure-12B). The effects (slopes) of both $PM_{2.5}$ and PM_c after excluding days with the extreme concentrations increased slightly and only the effect of $PM_{2.5}$ remained statistically significant in two-pollutant model (Table-12).

Sensitivity analysis restricted to emergency circulatory hospitalizations in TW region showed the risk estimates of $PM_{2.5}$ were slightly higher with wider confidence intervals, but remained statistically significant after adjustment for PM_c. We did not detect any statistical significant effects of PM_c in either single pollutant or two-pollutant model. Further adjustment for the gaseous pollutants showed that the effects of $PM_{2.5}$ or PM_c were quite sensitive to the inclusion of NO_2, but not of SO_2 or O_3 into the model (Table-12).

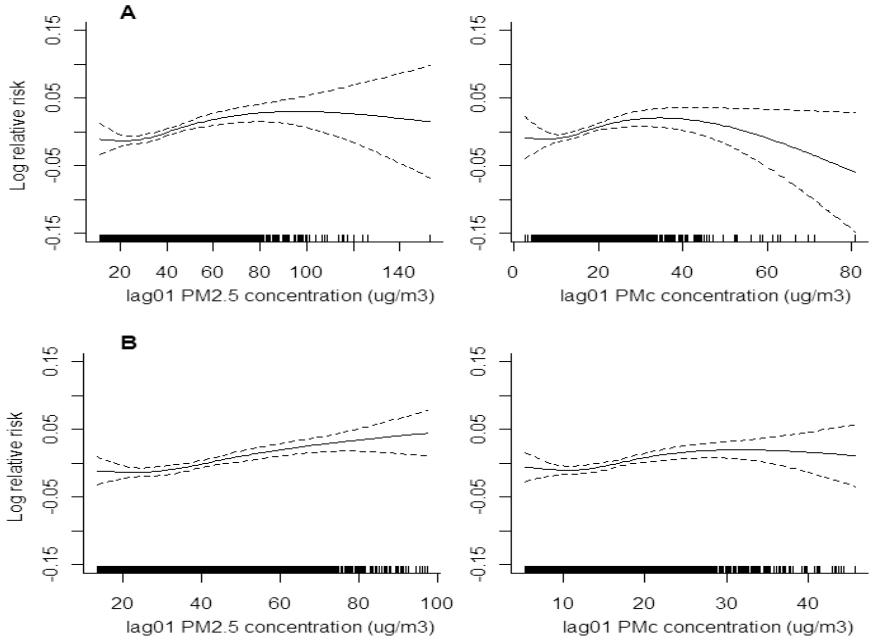

Figure- 12 Concentration-response curves between the logarithm of emergency hospital admission for total circulatory diseases and particle concentration (df=3).

The density of the vertical bars on the x-axis shows the distribution of pollutant concentration. The estimated mean percentage of change in daily admission is shown by the solid line, and the dotted lines represent twice the point-wise standard error. A: Analysis covered the entire range of $PM_{2.5}$ and PM_c concentration; B: Analysis restricted to 1% to 99% percentiles of lag_{01} PM_c (5.33-45.65 μg/m^3) and $PM_{2.5}$ (13.43-97.44 μg/m^3) concentration.

Table- 12 Percent increase (ERR% with 95%CI) of emergency hospital admissions for total circulatory diseases associated with an IQR increase in particle concentrations*

	Restrict analysis for PM in P_1~P_{99} [a]	Restrict analysis in TW residents [b]	Additionally adjusted for gaseous pollutants [c]		
			NO_2	SO_2	O_3
Single pollutant model					
$PM_{2.5}$	2.27 (1.35, 3.19)	2.97 (1.43, 4.54)	0.78 (-0.21, 1.78)	1.27 (0.39, 2.16)	2.23 (1.37, 3.10)
PM_c	1.45 (0.54, 2.36)	0.74 (-0.69, 2.19)	0.24 (-0.54, 1.02)	0.52 (-0.23, 1.28)	0.97 (0.22, 1.73)
Two pollutants model					
$PM_{2.5}$	2.16 (1.02, 3.31)	3.89 (1.95, 5.87)	0.86 (-0.30, 2.03)	1.36 (0.30, 2.44)	2.38 (1.32, 3.46)
PM_c	0.18 (-0.93, 1.30)	-1.40 (-3.14, 0.38)	-0.12 (-1.02, 0.80)	-0.14 (-1.04, 0.78)	-0.23 (-1.13, 0.69)

*: Average concentration of current day and previous 1 day (lag_{01}) was used to estimate the percent increase of emergency hospital admissions for total circulatory admissions based on an IQR increase of $PM_{2.5}$ (26.3μg/m^3) and PM_c (10.9μg/m^3). [a:] Analysis restricted to 1% to 99% percentiles of lag_{01} PM_c (5.33-45.65 μg/m^3) and $PM_{2.5}$ (13.43-97.44 μg/m^3) concentration; [b]: Analysis restricted to hospital admissions in Tsuen Wan residents; [c]: Analysis covered the entire range of PM concentration and city-wide circulatory admissions.

Figure-13 displays the percent increase of emergency circulatory hospital admissions associated with an IQR (26.3 $\mu g/m^3$) increase in lag_{01} concentrations of $PM_{2.5}$, with a range of different *df* choices for the smoother of time, temperature and relative humidity in two-pollutant models. Varying the *df* for time trend (within the range of 6-12 per year) and for weather conditions (within the range of 3-12) did not affect the regression results substantially, suggesting that the effect estimates of $PM_{2.5}$ and PM_c (results not shown) based on a *df* of 7 per year for time trend, a *df* of 6 for temperature and 3 for relative humidity were relatively robust in this respect.

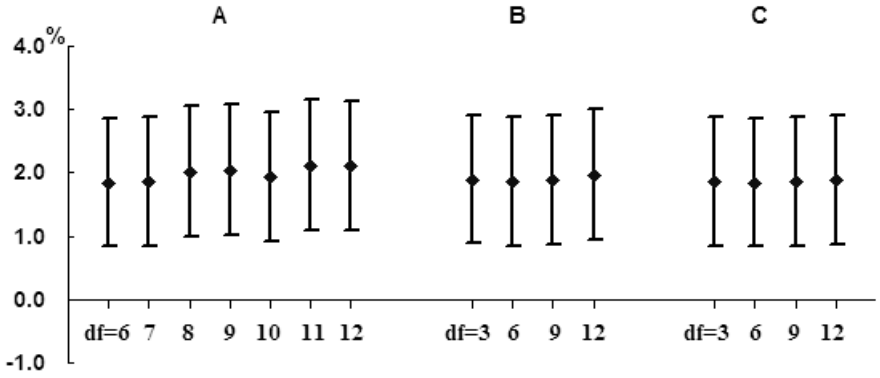

Figure- 13 Sensitivity analyses for varying df for time trend and weather conditions on emergency hospital admissions for total circulatory diseases based on an IQR increase of lag_{01} $PM_{2.5}$ concentrations.

A: df=6~12 per year for time trend; B: df=3~12 for current day and previous 3 days' mean temperature; C: df=3~12 for current day relative humidity.

3.4 Discussion

3.4.1 Main findings of this study

This study is one of the few that have investigated the associations between particulate matter pollution and cardio-respiratory hospitalizations that provided effect estimates for both $PM_{2.5}$ and PM_c simultaneously with the same time lag. We found significantly positive associations between both PM_c and $PM_{2.5}$ concentrations and increased emergency hospital admissions for respiratory diseases in Hong Kong. We also found the differential effects of fine and coarse particle fractions on cardiac hospitalizations, which showed the fine fraction to be more associated with cardiovascular outcomes than the coarse fraction. For the same particle fraction, the effect estimates differed according to the different subsets of cardio-respiratory diseases used, with the highest ERR for COPD in respiratory diseases or highest ERR for IHD in cardiovascular diseases. To our knowledge, this study is the largest single city study to date examining the effects of $PM_{2.5}$ and PM_c simultaneously on emergency cardio-respiratory hospitalizations, with almost a million of emergency hospital admissions spreading over a period of 6 years.

Unlike some studies which used every third or sixth day PM data (Lin et al. 2005; Peng et al. 2008), we used every day data and were able to estimate the effects of multiday average concentrations of $PM_{2.5}$ and PM_c, which were in general larger in magnitude than the effects of single day lags. Additionally this allowed for a more extensive examination of different lag structures, including both single-day lags and multiday lags. In single-pollutant models, we found positive associations on nearly all the lags examined between $PM_{2.5}$ and PM_c and emergency hospital admissions for

total respiratory diseases and COPD; total circulatory diseases, cardiac diseases and IHD. The estimated effect of PM_c on asthma appeared to be strongest several days after exposure, consistent with previous studies (Ko et al. 2007b; Lin et al. 2002). We did not find any significant associations between $PM_{2.5}$ and PM_c and cerebrovascular diseases. In joint $PM_{2.5}$ and PM_c two-pollutant models, the associations between PM_c and emergency hospital admissions remained statistically significant for respiratory diseases but not for circulatory diseases, while the effects of $PM_{2.5}$ were statistically significant for both respiratory diseases and circulatory diseases.

3.4.2 Compared with findings from the literature

A few studies examined the effects of PM_c on respiratory admissions after adjusting for $PM_{2.5}$ (Burnett et al. 1999; Chen et al. 2004; Ito 2003; Peng et al. 2008) but only one (Burnett et al. 1999) detected significant effects of PM_c independent of $PM_{2.5}$. However, unlike the daily measurements used in our study, daily levels of PM_c and $PM_{2.5}$ in that study were estimated from 6-day sampling and not directly measured. A few studies reported positive associations between PM_c and asthma hospitalizations in children, but the authors did not control the possible confounding effect from $PM_{2.5}$ (Lin et al. 2002; Tecer et al. 2008). Two recent studies demonstrated a significant increase in emergency hospital admissions for COPD and marginally significant increase for IHD on the day of dust storm events in Hong Kong, when the levels of coarse particles were very high, suggesting the adverse effect of coarse particles on lung health (Tam et al. 2012a; 2012b).

Our results were consistent with some previous studies that examined the effects of $PM_{2.5}$ and PM_c simultaneously on cardiovascular hospitalizations in six French cities (Host et al. 2008), in Toronto, Canada (Burnett et al. 1999), in central London

(Atkinson et al. 2010), and in Detroit, USA (Ito 2003). The concentrations of particles pollution in these cities were lower than those in Hong Kong, but the studies all supported significantly positive associations with both $PM_{2.5}$ and PM_c on respiratory admissions, while significantly positive associations with cardiovascular endpoints were found only for $PM_{2.5}$ but not PM_c. The largest NMMAPS conducted in 202 US urban counties found that short-term exposure to $PM_{2.5}$ increased the risk of hospital admissions for cardio-respiratory diseases (Dominici et al. 2006), while another NMMAPS using available data in 108 US counties failed to find any significant effects of PM_c on cardio-respiratory admissions (Peng et al. 2008). Even in the single-pollutant models, still some studies reported the non-significant effects of PM_c on cardiovascular admissions (Anderson et al. 2001; Halonen et al. 2009) or emergency visits (Metzger et al. 2004; Tolbert et al. 2000).

Englert suggested that the relative sizes of the effects attributed to fractions of PM_{10} depended on their relative mass percentages (Englert 2004). Considering that the mass percentage of PM_c to PM_{10} was in general rather low, the probability of finding significant associations with PM_c was also expected to be low. Although PM_c represented only about 30% of the PM_{10} mass concentration in our study, we estimated statistically significant ERRs for emergency respiratory hospital admissions in association with PM_c, which supports a specific effect of this PM fraction.

It is worthwhile noting that PM_c from different sources and with different chemical compositions in various study settings could also result in differing effects. The differences in associations estimated for Hong Kong and US populations (Chang et al. 2011; Peng et al. 2008) might be explained by differences in the compositions of

PM_c. Further studies are needed to examine the health effects of the specific components in PM_c.

3.4.3 Exposure windows selection and possible misclassification

Besides examining both single-day lags (lag_0~lag_5) and multi-day lags (lag_{01}~lag_{03}) in single-pollutant models, we focused on the biologically plausible effects of PM and chose the lag structure at lag_{03} for respiratory diseases and lag_{01} for circulatory diseases in two-pollutant models and sensitivity analyses (Anderson et al. 2001; Chen et al. 2004; Host et al. 2008). We selected the longer exposure window for respiratory hospitalizations because previous studies showed that respiratory diseases were more affected by PM pollution levels on the previous days, whereas cardiovascular diseases were more affected by same-day pollution (Braga et al. 2001; Linares and Diaz 2010). Using the average levels of lag_0 and lag_1 concentrations could have introduced an underestimation of the true relationships (Zanobetti et al. 2002), but avoids a potential bias resulting from multiple test and selectively reporting the most significant results (Anderson et al. 2005).

Possible misclassification in this study may include exposure misclassification and diseases misclassification. Exposure misclassification is a well-recognized limitation of time series air pollution studies, in which the aggregate monitoring data are used to represent the population exposure. In general, exposure misclassification tends to reduce the sensitivity of detecting the associations between air pollution and health outcomes. Zegar et al. have discussed three components of measurement error: a) an individual's deviation from the risk-weighted average personal exposure; b) the difference between the average personal exposure and the true ambient level; and c) the difference between the measured and the true ambient levels, which includes

spatial variation and instrument error. Authors argued that the first and third components are likely to have smaller effects on the relative risk estimates. However, the second component can be a source of substantial bias if, for example, there are short-term associations of the contributions of indoor sources with ambient concentrations (Zegar et al. 2000).

The patient data were collected from the computerized medical record system from Hong Kong Hospital Authority, which covered about 90% of all hospital beds in Hong Kong and included date and source of admission, and principal diagnosis on discharge coded with ICD-9, etc. We abstracted the daily count of hospital admissions for cardio-respiratory diseases with the ICD-9 codes as the principal diagnosis and through the accident and emergency services (emergency hospital admissions) as the health outcomes. The possibility of disease misclassification is low, as discharge coding was done by attending medical doctors and uniform ICD-9 codes were used throughout the study period. Even if diseases misclassification exists, it should be non-differential and would not influence the day to day variations.

3.4.4 Sensitivity analyses of main findings

The concentration-response relationships associated $PM_{2.5}$ and PM_c with emergency hospital admissions for total respiratory or circulatory diseases were almost linear after excluding the highest 1% and the lowest 1% extreme concentrations of $PM_{2.5}$ and PM_c, and the slopes increased slightly. Our results were robust and were not substantially modified by varying the degrees of freedom for the smoothers of time and weather conditions. Possible exposure misclassifications were examined by restricting emergency respiratory hospitalizations among residents living near the monitoring station, which were consistent with the overall results and provided

supports for using particulate matter data from a single central monitoring station in our main analyses. While similar restricted analysis was conducted for emergency circulatory diseases, we found the association with $PM_{2.5}$ was strengthened but the association with PM_c was attenuated. The results might suggest some more spatial variations and larger exposure misclassification for PM_c than $PM_{2.5}$, as previously studies indicated (Chang et al. 2011; Wilson and Suh 1997).

We have separately examined the possible confounding effects of the gaseous pollutants (NO_2, SO_2, O_3). We found that the effect sizes of $PM_{2.5}$ and PM_c on emergency respiratory hospital admissions changed very little with the inclusion of these three gaseous pollutants. We also found that the effect sizes of $PM_{2.5}$ and PM_c on emergency circulatory hospital admissions changed slightly with the inclusion of SO_2 or O_3 into the model. However, the associations with both $PM_{2.5}$ and PM_c were no longer significant when NO_2 was included in the models, showing the effects of particles pollution on cardiovascular hospitalizations were not independent of NO_2. Few previous studies examined the PM effects on cardio-respiratory hospitalizations after adjustment for the gaseous pollutants and got the similar results (Burnett et al. 1997; Chen et al. 2004, 2005; Lin et al. 2002, 2005). The correlation coefficients (r) between $PM_{2.5}$, PM_c and NO_2 (r=0.785 and 0.557 respectively) were quite high in Hong Kong, while the correlations between PM and SO_2 or O_3 were rather lower, which would partly explain the results. Another possible reason might be due to the stronger health effect of NO_2 than particulate matter on cardiovascular hospitalizations in Hong Kong, as several previous studies indicated (Wong CM et al. 2001; Wong TW et al. 2006).

3.4.5 Biological mechanisms of the differential effects of fine and coarse particles

The biological mechanisms underlying the differential effects of $PM_{2.5}$ and PM_c on cardio-respiratory emergency hospitalizations might be relevant to the sites of deposition in the respiratory tract and the chemical composition of these two factions. Compared with PM_c, $PM_{2.5}$ has higher number concentrations, larger surface area and better lung deposition. PM_c do not penetrate as deeply into the respiratory tract as $PM_{2.5}$ and so more likely to affect the upper and larger airways. PM_c originate mainly from the soil and abrasive mechanical processes, and thus may also carry biological materials such as bacteria, moulds or pollens, and are therefore likely to produce adverse health effects in the respiratory system (Almeida et al. 2006). $PM_{2.5}$ which is mainly coming from combustion processes has a much greater probability of reaching the small airways and the alveoli of the lung. Particles in the alveolar region are cleaned more slowly than in the conducting airways, which may be one reason for the greater toxic effect of $PM_{2.5}$. Researchers also found that inhaled ultrafine particles could even translate rapidly from the lungs into the blood circulation in humans and thus influence cardiovascular endpoints more directly (Nemmar et al. 2002).

Evidences from toxicological studies showed that on an equal mass basis, $PM_{2.5}$ and PM_c both produce pulmonary inflammation and oxidative stress, which could lead to both respiratory and cardiovascular damage (Pozzi et al. 2003; Shi et al. 2003). A study examined the different biological activity of $PM_{2.5}$ and PM_c revealed that hemolytic potential was greater for $PM_{2.5}$ than for PM_c in equal mass concentration (Diociaiuti et al. 2001). The biological mechanisms underlying the associations

between $PM_{2.5}$ and cardiac diseases also involved modulation of autonomic nervous activity by decreasing heart rate variability (Gold et al. 2000) and increase of circulating fibrinogen and blood coagulability (Schwartz 2001). An experimental study revealed that exposure of mice to PM_c resulted in significant pulmonary toxicity while ultrafine PM appeared to enhance cardiac ischemia/reperfusion injury (Tong et al. 2010), which would support our findings.

3.4.6 Limitations of this study

Some limitations of the current study should be noted. We estimated PM_c concentrations by subtracting $PM_{2.5}$ from PM_{10} measurements. A disadvantage of this method is that PM_c exposure estimates are subjected to two sources of random error in measurement (standard error) rather than one, which may reduce the statistical power of detecting an association. However, we were still able to detect significant associations between PM_c and emergency respiratory hospital admissions in Hong Kong.

As in other time-series studies, we used available outdoor monitoring data to represent the population exposure to ambient particles. Indoor air pollution and personal exposure data were not available. A simulation using data from a recent multi-pollutant ($PM_{2.5}$, O_3, and NO_2) exposure assessment study conducted in Baltimore, Maryland suggested that for $PM_{2.5}$, ambient concentrations available from local monitoring stations might be adequate surrogates for the corresponding total personal exposures (Schwartz et al. 2007). On the other hand, PM_c levels tend to be less spatially homogeneous than $PM_{2.5}$ because of shorter travelling distance and suspending time in the atmosphere (Monn 2001), increasing the likelihood that personal exposure will be misclassified in monitor-based studies of ambient PM_c.

However in our current study, the undetectable association between PM_c and cardiac hospitalizations should not be probably due to the exposure misclassification because the sensitivity analyses restricted to 1% to 99% percentiles of particle concentrations or hospital admissions in residents living near the monitoring station also did not detect any significant effects of PM_c independent of $PM_{2.5}$.

3.5 Conclusion and recommendations

In conclusion, we differentiated the effects of $PM_{2.5}$ and PM_c on emergency hospital admissions in Hong Kong, which showed the significantly positive associations with both $PM_{2.5}$ and PM_c on respiratory diseases and the much stronger and significantly positive associations with $PM_{2.5}$ than PM_c on cardiac diseases. Our findings confirmed the adverse effects of $PM_{2.5}$ on cardio-respiratory hospitalizations and added to the growing body of literature about the adverse health effects of PM_c and the different effects of two fractions of PM_{10}. Further studies are needed to elucidate the toxicological differences linked to the different chemical compositions of $PM_{2.5}$ and PM_c under different settings of time and place, as well as to identify the component(s) posing the greatest health risk.

Chapter 4 Joint effects/Interactions of PM_{10} and gaseous pollutants

4.1 Objectives

The Specific objectives of this part of study were as follows:

1. To examine the joint effects of particulate matter and gaseous pollutants one by one on emergency hospital admissions for cardio-respiratory diseases in Hong Kong, after accounting for time trend, weather conditions and influenza outbreaks;

2. To explore the possible interactions between particulate matter and gaseous pollution.

4.2 Materials and Methods

4.2.1 Data on air pollution and meteorology variables

We collected air pollution concentrations from 1 January 1998 to 31 December 2007 from the Environmental Protection Department (EPD). There are totally 11 general monitoring stations and 3 roadside stations interspersed in different districts of Hong Kong. We excluded roadside stations and one general station located on a remote isolate island which reflects the air quality of background environment, and leaving 10 general monitoring stations to generate daily mean air pollution concentrations.

We calculated daily 24-hr mean concentrations of PM_{10}, NO_2 and SO_2, and daytime 8-hr (10:00–18:00 hours) mean concentration of O_3 from the EPD database. We defined daily concentrations as non-missing for each monitoring station if at least 18 of 24 hourly concentrations of each pollutant were available. We first centered

non-missing daily means for each station *i,* that is, subtracting individual daily concentrations (X_{ij}) by an annual station mean (X_i) for each day *j*. We then combined the centered data from all stations and added them by the annual mean of all stations (X) to form $X'_{ij} = (X_{ij} - X_i + X)$. At last we computed the daily (mean) concentrations of individual pollutants for analysis by taking the mean of centered X'_{ij} over all stations (Wong CM et al. 2001).

We collected daily mean temperature and relative humidity for the same period from the Hong Kong Observatory.

4.2.2 Data on emergency hospital admissions for cardio-respiratory diseases

We collected city wide emergency hospital admissions (admissions through the accident and emergency services) for cardio-respiratory diseases in Hong Kong from 1 January 1998 to 31 December 2007. The records of admission were taken from the publicly funded hospitals providing 24 hours accident and emergency services and covering 90% of hospital beds in Hong Kong for local residents (Wong TW et al. 1999). Patient data captured from the computerized medical record system included age, date of admission, source of admission, hospital, residential address and principal diagnosis on discharge coded with *International Statistical Classification of Diseases, 9th Revision* (ICD-9; (WHO 1975)).

We chose the following hospital admissions through the accident and emergency services for diseases as the health outcomes:

- Diseases of the respiratory system (RES, ICD-9:460-519), and its subsets

- Chronic obstructive pulmonary diseases (COPD, ICD-9: 491, 492, 496);
- Asthma (ICD-9: 493);
- Pneumonia (ICD-9: 480-486);

- Diseases of the circulatory system (CIR, ICD9:390-459), and its subsets
  - Cardiac diseases (HD, ICD-9: 390-429);
    - Ischemic heart diseases (IHD, ICD-9: 410-414);
  - Cerebrovascular diseases (CBD, ICD-9: 430-438).

We excluded influenza (ICD-9:487.0-487.8) from total respiratory diseases because previous studies demonstrated that influenza outbreak is a potential confounder in the data analysis (Ren et al. 2006; Thach et al. 2010).

4.2.3 Statistical models

4.2.3.1 Core model set up

We set up the core generalized additive Poisson models following the same strategies described in section 3.2.3.1, but being a little bit more conservative in model specification and *df* choosing. Briefly, a core model was set up to remove the long term trends, seasonal variations and adjust for time varying confounders as follows:

$$log(E(Y)) = \alpha + s(t, df=8/year \times no.\ of\ years) + s(Temp_0, df=6) + s(Temp_{1-3}, df=6) + s(Humid_0, df=3) + s(Humid_{1-3}, df=3) + \beta_1 \times DOW + \beta_2 \times Holiday + \beta_3 \times influenza \ldots\ldots\ldots\ldots [5]$$

Here *E(Y)* means the expected daily emergency hospital admission counts on day t; *s(.)* is the smoothing spline function for nonlinear variables. β is regression coefficient. The residuals of the core model were examined to check whether there were discernable patterns and autocorrelation by means of the residual plot and the

PACF plot. If the PACF of the residuals of the core model [5] was larger than 0.1 for some lags, we added autoregressive terms of outcome variable into core model [5] to remove the serial correlation of residuals, in an effort to control for any confounding effect caused by omitted time-dependent covariates (Kan et al. 2010; Wong CM et al. 2008b).

4.2.3.2 Three parallel time series models

We used three parallel time series approaches to examine the joint effects and interactions between PM_{10} and gaseous pollutants. Interaction detection between PM_{10} and NO_2 was illustrated in the following paragraphs. Interactions between PM_{10} and O_3, or between PM_{10} and SO_2 were examined following the same approaches.

Firstly, we used the nonparametric bivariate response model to identify the joint effect of PM_{10} and NO_2 on each health outcome (Ren et al. 2006; Roberts 2004). This model provided a picture of the joint response surface of two predictors (PM_{10} and NO_2) on the dependent variable (emergency hospital admissions for each subset of circulatory diseases). We used it to observe graphically whether or not there was an interactive effect of two continuous predictors. We added *lo( )* for PM_{10} and NO_2 which was the two-dimensional smooth response surface controlled by the smooth parameter *span* into the core model:

$$log(E(Y)) = \alpha + lo(pm_{10}, no_2, span=0.25) + COVs \ldots\ldots\ldots\ldots\ldots\ldots [6]$$

Where *lo(.)* refered to local regression smoothing spline (LOESS) and $lo(pm_{10}, no_2, span=0.25)$ displayed the joint effect of PM_{10} and NO_2 exposure on current day. *COVs* were all time varying confounders identified in the core model [5].

Secondly, we categorized the concentration of PM_{10} and NO_2 into three levels (low, medium and high), using tertiles (33.3^{th} and 66.7^{th} percentiles) as the cutoff points. We created a new variable *PNlevel* to denote the nine different combinations of PM_{10} and NO_2 as a mixture (Table-13). Then we added *PNlevel* as dummy variables into core model [5] to estimate the joint effect of PM_{10} and NO_2 as a mixture (so called joint effect model) (Tse et al. 2011; Wang et al. 2009), using the combination of low levels of PM_{10} and NO_2 as the reference group. The individual and the joint effects of PM_{10} and NO_2 were estimated approximately in this way.

$$log(E(Y)) = \alpha + factor(PNlevel) + COVs \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots [7]$$

Table- 13 *PNlevel* created to denote the joint exposure of PM_{10} and NO_2

PM_{10} level*	***NO_2 level****	***PNlevel***	Remarks
Low	Low	P_1N_1	Reference group (RR_{11}=1)
Medium	Low	P_2N_1	
High	Low	P_3N_1	Individual PM_{10} exposure approximately (RR_{31})
Low	Medium	P_1N_2	
Medium	Medium	P_2N_2	
High	Medium	P_3N_2	
Low	High	P_1N_3	Individual NO_2 exposure approximately (RR_{13})
Medium	High	P_2N_3	
High	High	P_3N_3	Joint exposure of PM_{10} and NO_2 approximately (RR_{33})

*: Tertiles were the cutoff points: 35.80 and 60.88 μg/m^3 for PM_{10}, and 48.06 and 64.41 μg/m^3 for NO_2 respectively.

Synergism is defined as occurring if the effect of the combination is greater than the sum of individual effects, while antagonism is occurred if the effect of the combination is less than the sum of individual effects (Mauderly and Samet 2009). The concept of synergism or antagonism is the interaction on additive scale.

Rothman suggested that interaction as departure from additive model rather than multiplicative model better reflects the biological interaction (Rothman KJ et al. 2008). We defined the synergy index (SI) as follows (Tse et al. 2011):

$$SI = \frac{(RR_{33} - 1)}{(RR_{13} - 1) + (RR_{31} - 1)} = \frac{ERR_{33}}{ERR_{13} + ERR_{13}}$$

Note that subtracting 1 from each RR provides an estimate of the excess relative risk (ERR) of hospital admissions in each group above that in the reference group of relatively low exposure. SI greater than 1 shows potential synergism, while SI less than 1 shows potential antagonism.

Finally, we applied a parametric stratified model (Ren et al. 2006, 2008a, 2008b) to examine the effects of PM_{10} across different NO_2 levels (three levels with tertiles as the cutoff points) by adding the product term between PM_{10} concentrations (as continuous variable) and NO_2 level (as categorical variable). Similarly, we estimated the effects of NO_2 across different levels of PM_{10} by adding the product term between NO_2 concentrations (continuous) and PM_{10} level (categorical).

$$log(E(Y)) = \alpha + pm_{10} \times factor(no_2\ level) + COVs \quad \ldots\ldots[8]$$

$$log(E(Y)) = \alpha + no_2 \times factor(pm_{10}\ level) + COVs \quad \ldots\ldots[9]$$

In model [8] and [9], we estimated relative risks (RRs) and confidence intervals using the method that incorporated the coefficient of the pollutant and the covariance of the pollutant and the interaction term (Figueiras et al. 1998; Lipsett et al. 1997). Based on these two models, we detected the modified effect of NO_2 on PM_{10} or the modified effect of PM_{10} on NO_2.

We expressed the effect estimates for pollutants as continuous variables in terms of the percentage increase (Excess Relative Risk, ERR (%)) in emergency hospital admissions for circulatory diseases for a 10 $\mu g/m^3$ increment of pollutant concentrations, and respective 95% confidence intervals (95%CI). We also expressed the effect estimates for the combinations of different PM_{10} and NO_2 levels as excess relative risks (ERR%) and 95%CI, compared with the combination of low levels of PM_{10} and NO_2 as reference. We conducted all analyses in statistical environment R2.11.1 (R Development Core Team, 2011: http://www.r-project.org).

4.3 Results

4.3.1 Air pollution concentrations and meteorological factors

Figure 14 shows the time series of daily mean air pollution concentrations, temperature and relative humidity. During our study period, the daily mean concentration of air pollutants was 52.8 $\mu g/m^3$ for PM_{10}, 58.0 $\mu g/m^3$ for NO_2, 19.5 $\mu g/m^3$ for SO_2, and 39.8 $\mu g/m^3$ for O_3 (Table-14). We also displayed the distributions of PM_{10} concentration across the low, medium and high levels of the three gaseous pollutants in Table-14. The daily mean temperature in Hong Kong was 23.6 centigrade with relative humidity around 78.1%. The correlation between PM_{10} and NO_2 was high with a correlation coefficient 0.759. The correlation was moderate with a correlation coefficient 0.428 between PM_{10} and SO_2, and 0.591 between PM_{10} and O_3 (Table-15).

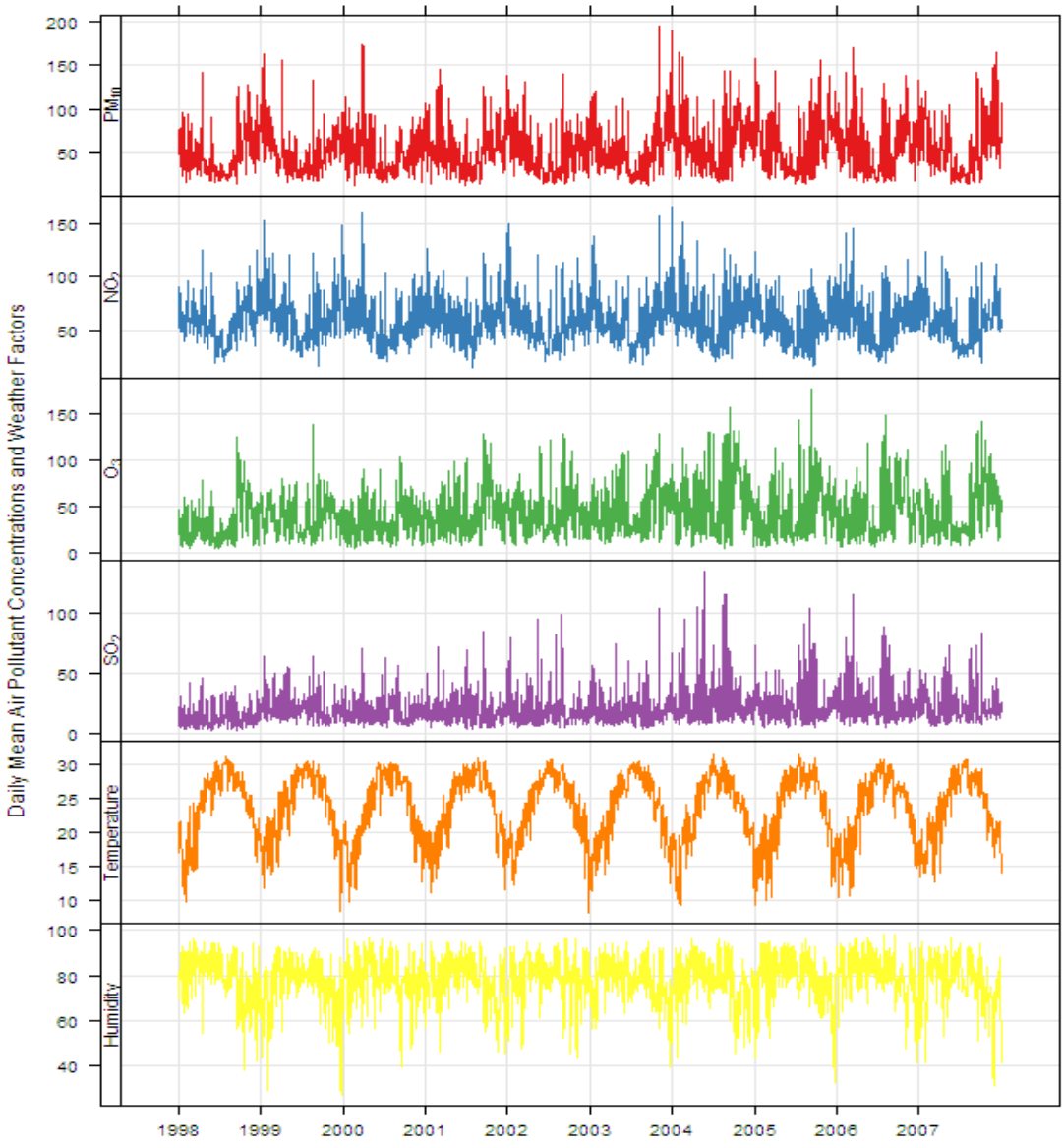

Figure- 14 Daily Time Series of Air Pollution Concentrations and Weather Factors

Table- 14 Distribution of air pollution concentrations and weather conditions in Hong Kong from 1998 to 2007 (n=3652)

Variables	Mean	SD	Percentiles						
			Min.	10th	25th	50th	75th	90th	Max.
Pollution concentration (μg/m^3)									
PM_{10}	52.8	26.9	14.0	23.7	31.2	47.1	69.0	90.5	196.0
PM_{10} in low NO_2	*30.3*	*10.8*	*14.0*	*19.6*	*23.0*	*28.1*	*34.8*	*43.5*	*114.3*
PM_{10} in medium NO_2	*52.5*	*20.2*	*17.6*	*31.0*	*38.1*	*48.4*	*62.7*	*78.2*	*154.9*
PM_{10} in high NO_2	*75.5*	*25.0*	*18.8*	*46.4*	*57.6*	*72.2*	*90.4*	*106.6*	*196.0*
PM_{10} in low O_3	*37.0*	*19.8*	*14.0*	*20.2*	*24.0*	*30.9*	*43.0*	*62.4*	*170.1*
PM_{10} in medium O_3	*49.0*	*22.0*	*14.6*	*25.6*	*32.7*	*44.5*	*61.7*	*79.5*	*188.3*
PM_{10} in high O_3	*72.4*	*25.6*	*24.7*	*42.5*	*53.1*	*69.0*	*88.1*	*105.0*	*196.0*
PM_{10} in low SO_2	*41.9*	*18.3*	*14.0*	*20.5*	*27.1*	*39.0*	*52.5*	*67.6*	*114.3*
PM_{10} in medium SO_2	*53.8*	*24.4*	*16.4*	*25.3*	*33.5*	*50.9*	*70.0*	*86.9*	*155.9*
PM_{10} in high SO_2	*62.6*	*32.1*	*17.3*	*26.1*	*33.9*	*58.2*	*85.1*	*104.8*	*196.0*
NO_2	58.0	20.5	14.9	32.7	43.5	56.2	69.1	84.9	168.2
SO_2	19.5	13.2	1.8	8.0	11.0	16.3	23.7	33.8	134.9
O_3	39.8	24.3	2.3	14.6	21.1	34.0	54.0	72.8	180.0
Meteorology factors									
Temperature (^{o}C)	23.6	4.9	8.2	16.5	19.7	24.8	27.8	29.3	31.8
Relative humidity (%)	78.1	10.0	27.0	65.0	73.0	79.0	85.0	90.0	98.0

Abbreviations: SD-standard deviation; Min.-minimum; Max.-maximum.

Table- 15 Pearson Correlation coefficients between pollution concentrations and weather conditions in Hong Kong, 1998-2007 (n=3652)*

Variables	PM_{10}	NO_2	SO_2	O_3	Temperature
PM_{10}	1.000				
NO_2	0.759	1.000			
SO_2	0.428	0.528	1.000		
O_3	0.591	0.424	0.173	1.000	
Temperature	-0.361	-0.382	0.117	0.027	1.000
Relative humidity	-0.493	-0.328	-0.168	-0.518	0.216

*: All correlation coefficients are statistically significant (P<0.001), except the correlation coefficient between O_3 and temperature (p=0.101).

4.3.2 Emergency hospital admissions for cardio-respiratory diseases

Figure 15 shows the time series of daily mean emergency hospital admissions for respiratory diseases and circulatory diseases.

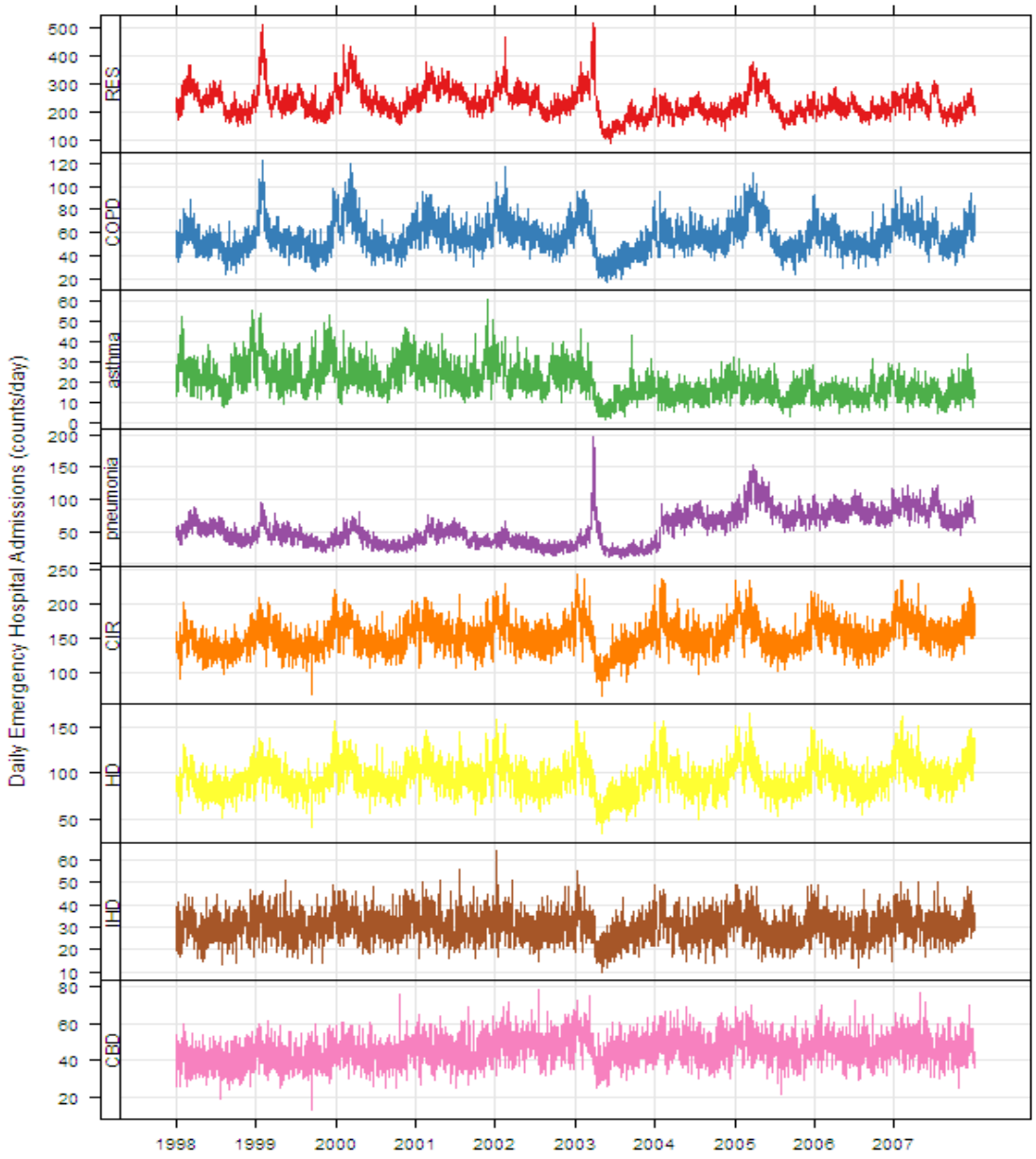

Figure- 15 Daily Time Series of Emergency Hospital Admissions

A total of 858,184 and 561,561 emergency hospital admissions for diseases from respiratory system and circulatory system were recorded respectively in our study population. Among the respiratory admissions, 24.0% was COPD, 8.4% was asthma, and 23.6% was pneumonia. On average, there were 56.4, 19.7, 55.5 emergency hospital admissions per day for COPD, asthma and pneumonia respectively. Among the circulatory admissions, 62.0% were HD, 19.6% was IHD, and 29.8% was CBD. On average, there were 95.3, 30.2, 45.8 emergency hospital admissions per day for HD, IHD, and CBD respectively (Table-16).

Table- 16 Distribution of Emergency Hospital Admissions for Cardio-respiratory Diseases in Hong Kong, 1998-2007 (3652 days)

Hospital				Percentiles					
Admissions	Mean	SD	Min	10th	25th	50th	75th	90th	Max
Emergency respiratory admissions									
All RES	235.0	51.1	89	181	200	227	263	299.9	518
COPD	56.4	14.4	17	40	46	55	65	76	122
asthma	19.7	8.2	1	10	14	19	25	31	61
pneumonia	55.5	25.9	9	25	34	52	74	90	197
Emergency circulatory admissions									
All CIR	153.8	23.4	66	126	138	152	168	184	243
HD	95.3	17.8	34	75	83	94	106	119	165
IHD	30.2	6.6	10	22	26	30	34	39	64
CBD	45.8	8.0	13	36	40	46	51	56	79

Abbreviations: SD-standard deviation; Min.-minimum; Max.-maximum; RES-all respiratory diseases excluding influenza; COPD-chronic obstructive pulmonary diseases; CIR-all circulatory diseases; HD- cardiac diseases; IHD- ischemic heart diseases; CBD- cerebrovascular diseases.

4.3.3 Results from single-pollutant model

4.3.3.1 Pollution effects on emergency hospital admissions for respiratory diseases

The effects of four criteria pollutants were estimated on current day (lag_0) exposure up to previous 1-5 days (lag_1-lag_5) in single pollutant models. Figure-16 shows the effects of pollutants for emergency hospital admissions for all respiratory diseases and its three selected subsets (COPD, asthma and pneumonia), respectively. In general, we detected statistically significant associations between air pollution and respiratory hospitalizations, especially for COPD.

The greatest single-lag effect for PM_{10} was found on current day (lag_0) on emergency hospital admissions for total respiratory diseases, with an ERR (%) of 0.24% (95% CI: 0.11-0.36%) for a 10 $\mu g/m^3$ increment of PM_{10} concentrations. The greatest single-lag effects for NO_2 and SO_2 were found for exposure 3 days before (lag_3), with an ERR (%) of 0.40% (95% CI: 0.25-0.55%) and 0.27% (95% CI: 0.06-0.49%) for a 10 $\mu g/m^3$ increment of NO_2 and SO_2 concentrations, respectively. The greatest single-lag effect for ozone was found on previous one day (lag_1), with an ERR (%) of 0.70% (95% CI: 0.57-0.83%) for a 10 $\mu g/m^3$ increment of ozone concentrations. The greatest lag effects for the four criteria pollutants on the three subsets of respiratory diseases were not consistent. To avoid the potential bias resulting from selectively reporting the most significant results, and to make the interactions easier to understand and interpret, we used the same lag_0 exposure of all four pollutants in the further analysis on the interactions detection.

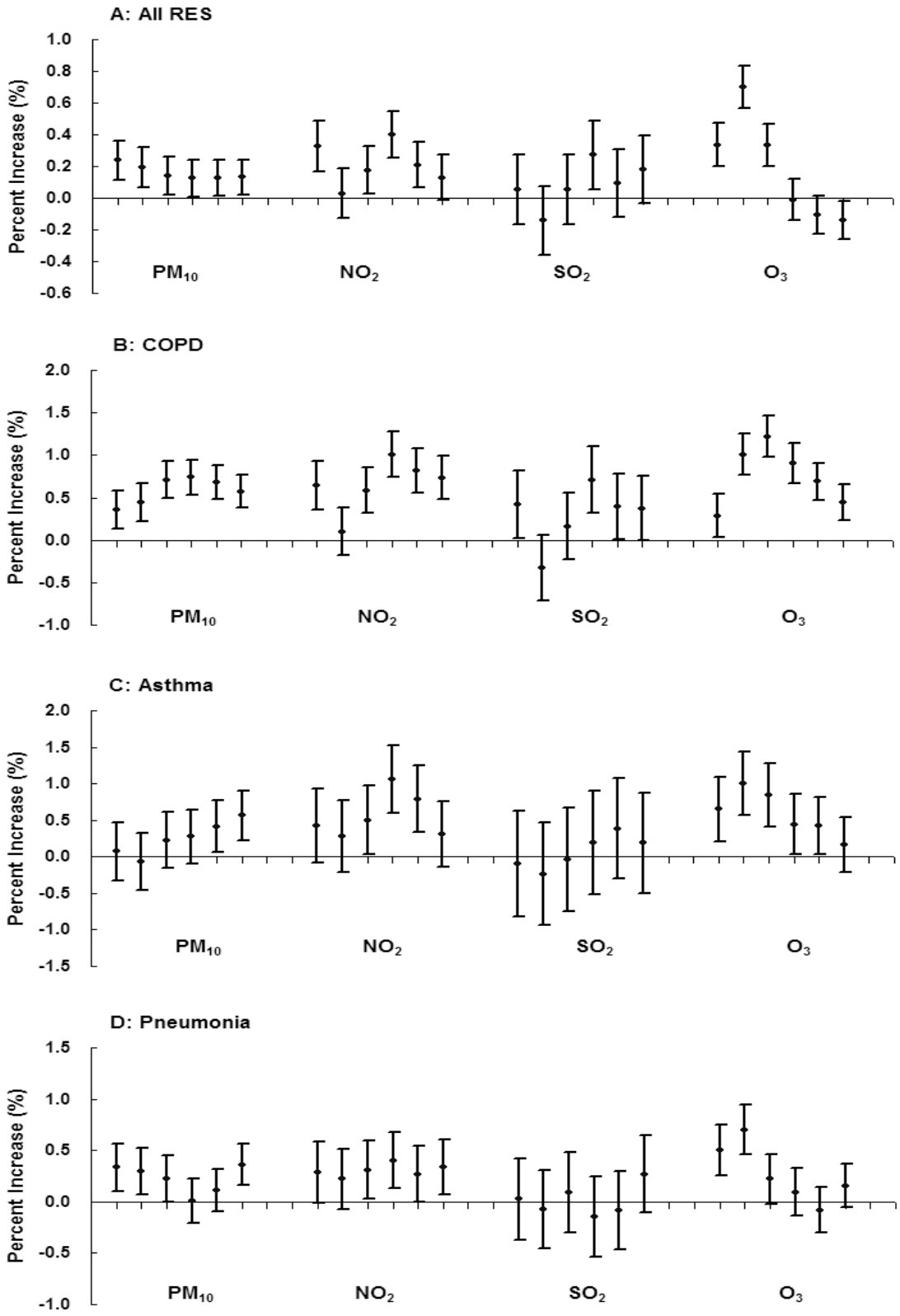

Figure- 16 Percent increase (ERR % with 95%CI) in emergency hospital admissions due to total respiratory diseases, COPD, asthma and pneumonia for 10-µg/m^3 increase in pollution concentrations on different lag days (lag_0-lag_5)

4.3.3.2 Pollution effects on emergency hospital admissions for circulatory diseases

The effects of the four criteria pollutants were also estimated on current day (lag_0) exposure up to previous 1-5 days (lag_1-lag_5) with single pollutant models for all circulatory diseases and its three selected subsets (cardiac diseases, IHD and cerebrovascular diseases). Figure-17 shows the effects of the pollutants on emergency hospital admissions for all circulatory diseases and its three subsets, respectively.

The greatest single-lag effects for PM_{10}, NO_2 and SO_2 on emergency hospital admissions for all circulatory diseases were on current day (lag_0), associated with an ERR (%) of 0.39% (95% CI: 0.25-0.53%), 0.78% (95% CI: 0.60-0.96%), and 0.65% (95% CI: 0.40-0.90%) for a 10 $\mu g/m^3$ increment of lag_0 PM_{10}, NO_2 and SO_2 concentrations respectively. The effects of ozone were similar on lag_1 to lag_4, with an ERR (%) of around 0.25% (95% CI: 0.09-0.40%) for a 10 $\mu g/m^3$ increment of ozone exposure. The greatest lag effects for the three subsets of diseases were in a little difference. To avoid the potential bias resulting from selectively reporting the most significant results, and to make the interactions easier to understand and interpret, we used the same lag_0 exposure of all four pollutants in the further analysis on the interactions detection.

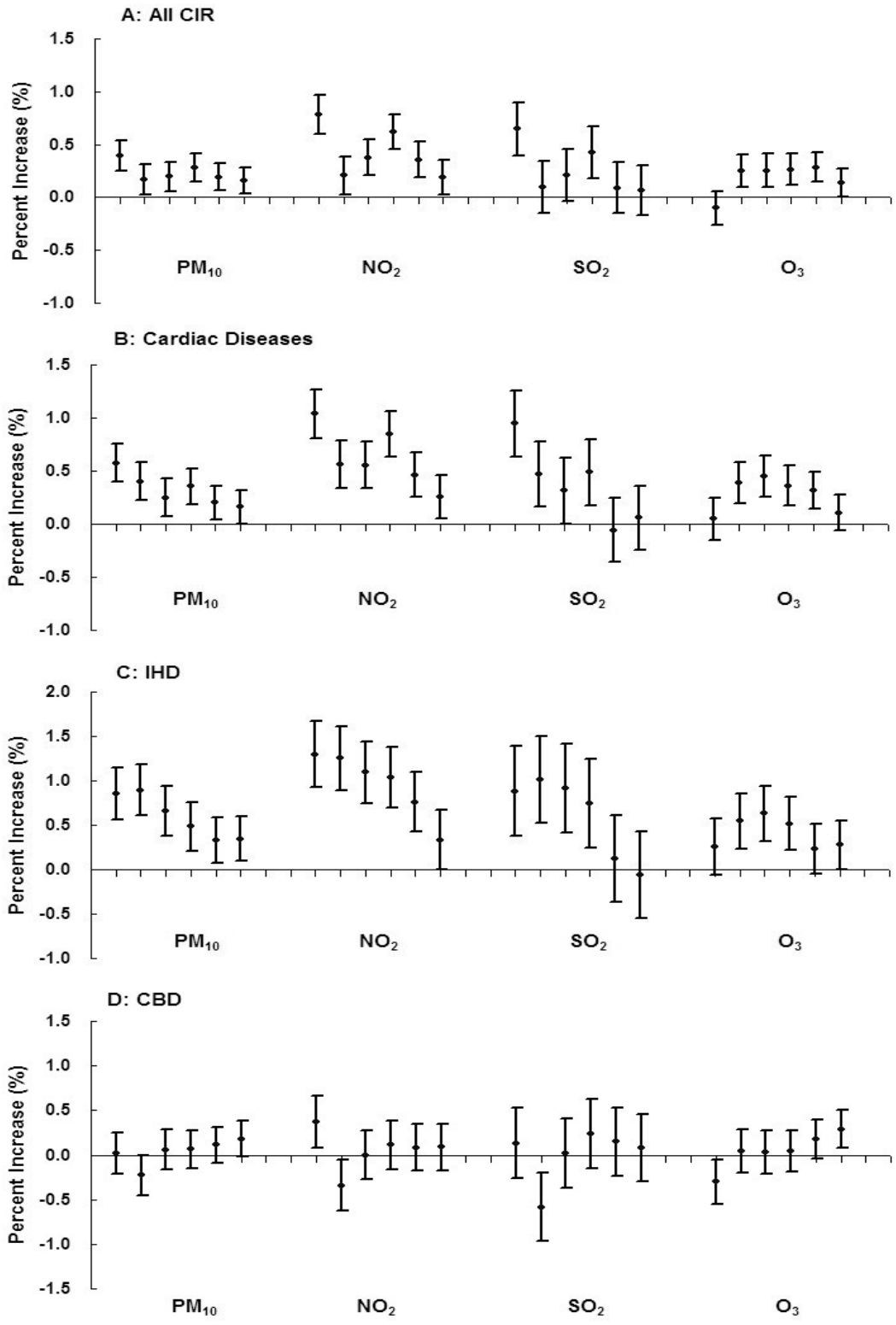

Figure- 17 Percent increase (ERR % with 95%CI) in emergency hospital admissions due to total circulatory diseases, cardiac diseases, IHD and cerebrovascular diseases for 10-µg/m^3 increase in pollution concentrations on different lag days (lag_0-lag_5)

4.3.4 Joint effects/Interactions between PM_{10} and NO_2 on cardio-respiratory hospitalizations

To explore the potential interactions between PM_{10} and NO_2 on emergency hospital admissions for circulatory diseases, we fitted the bivariate response surface models to display the joint effects of PM_{10} and NO_2 (Figure-18), using current day (lag_0) pollution concentrations as continuous variables. Results showed that the joint effect patterns of PM_{10} and NO_2 were very similar on emergency hospital admissions for CIR, HD and IHD, less so for CBD, COPD, asthma and pneumonia, and displayed another pattern for RES. Response surfaces showed some possible interactions between PM_{10} and NO_2 on cardio-respiratory hospitalizations.

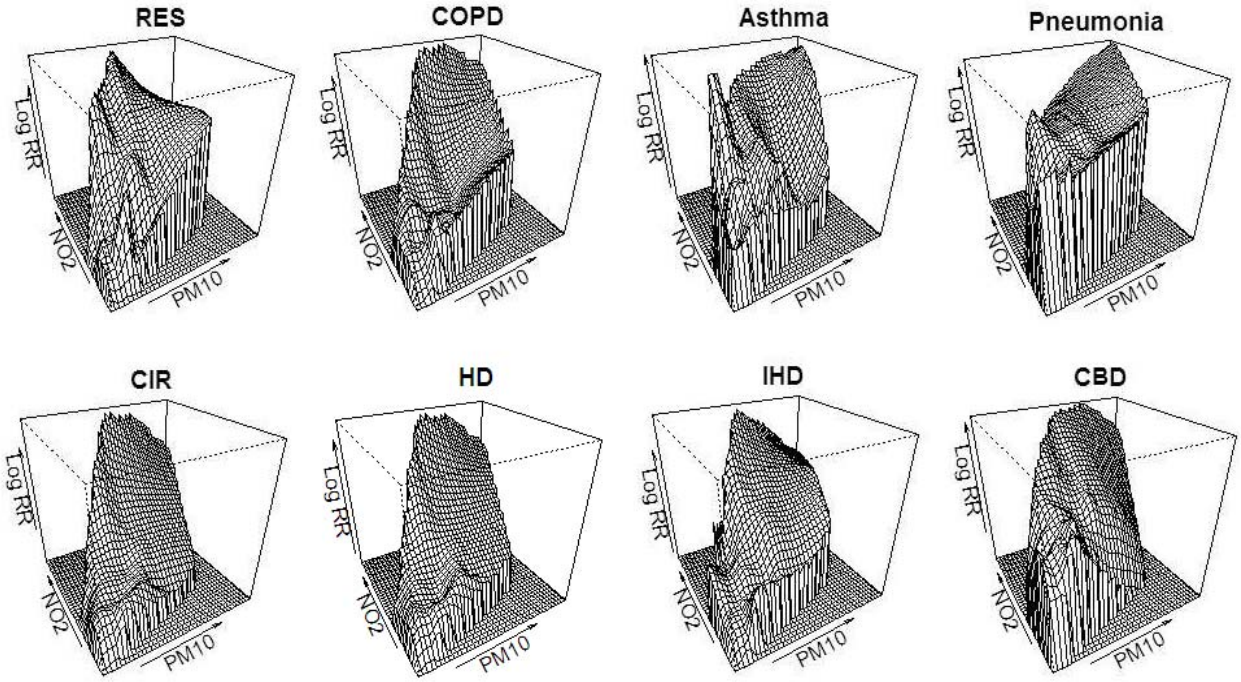

Figure- 17 Bivariate Response Surfaces of Current Day PM_{10} and NO_2 on Emergency Cardio-Respiratory Hospital Admissions

We created *PNlevel* to denote the different combinations of PM_{10} and NO_2 levels and used the joint effect models to explore the joint effects of particles pollution and nitrogen dioxide as a mixture, setting the combination of low levels of PM_{10} and NO_2 as the reference group. We found the greatest and statistically significant joint effects in the combination when PM_{10} and NO_2 concentrations were both in high levels on emergency hospital admissions for CIR, HD and IHD (ERR%=2.73, 4.09 and 6.85, respectively), but not for CBD (Table-17). The synergy indices (SI) for these three categories of circulatory outcomes were 3.27, 4.56 and 2.42, respectively. Results showed there might be some synergism between PM_{10} and NO_2 for cardiac hospitalizations, especially for HD hospital admissions. However, the results were not so consistent on the joint effects of PM_{10} and NO_2 for respiratory hospitalizations. The greatest joint effects were found on the days when high PM_{10} concentrations combined with medium NO_2 for RES and COPD, or the days when medium PM_{10} concentrations combined with high NO_2 for asthma and pneumonia. The synergy indices (SI) for these four categories of respiratory outcomes were less than or around 1 with the lowest value 0.43 for COPD, which showed some potential antagonism between PM_{10} and NO_2 on COPD hospitalizations.

Table- 17 The Joint Effects of Particles Pollution and Nitrogen Dioxide (ERR% with 95%CI)* on the Emergency Hospital Admissions for Cardio-respiratory Diseases

PM_{10}	NO_2	PN level	No.of Days	RES	COPD	Asthma	Pneumonia	CIR	HD	IHD	CBD
Low	Low	P_1N_1 [a]	944	0	0	0	0	0	0	0	0
Medium	Low	P_2N_1	248	1.32 (0.38, 2.28)	2.31 (0.35, 4.31)	2.26 (-1.08, 5.72)	1.63 (-0.28, 3.57)	-0.06 (-1.23, 1.12)	-0.72 (-2.20, 0.80)	0.98 (-1.67, 3.70)	1.48 (-0.64, 3.63)
High	Low	P_3N_1 [b]	24	0.69 (-2.04, 3.49)	3.54 (-1.92, 9.32)	1.43 (-8.19, 12.06)	2.93 (-2.25, 8.39)	-1.46 (-4.75, 1.94)	-0.96 (-5.15, 3.42)	-1.35 (-8.77, 6.67)	-4.18 (-9.92, 1.94)
Low	Medium	P_1N_2	239	0.05 (-0.91, 1.02)	0.80 (-1.20, 2.84)	-0.86 (-4.14, 2.53)	-0.24 (-2.26, 1.82)	-0.37 (-1.57, 0.85)	-0.14 (-1.67, 1.41)	1.04 (-1.68, 3.83)	-0.81 (-2.98, 1.40)
Medium	Medium	P_2N_2	640	0.34 (-0.37, 1.06)	1.14 (-0.35, 2.65)	1.01 (-1.48, 3.57)	-0.56 (-2.04, 0.93)	0.41 (-0.48, 1.30)	0.12 (-1.01, 1.26)	1.39 (-0.62, 3.44)	0.52 (-1.09, 2.16)
High	Medium	P_3N_2	341	**1.98 (1.06, 2.92)**	**2.66 (0.78, 4.58)**	0.24 (-2.88, 3.46)	1.72 (-0.12, 3.60)	0.97 (-0.15, 2.10)	1.25 (-0.18, 2.70)	1.27 (-1.28, 3.88)	0.41 (-1.63, 2.48)
Low	High	P_1N_3 [c]	33	1.48 (-0.78, 3.80)	1.44 (-3.14, 6.24)	0.16 (-7.35, 8.29)	-1.01 (-5.74, 3.96)	2.30 (-0.53, 5.21)	1.86 (-1.69, 5.53)	-1.48 (-7.69, 5.13)	2.05 (-3.12, 7.49)
Medium	High	P_2N_3	332	1.57 (0.68, 2.47)	1.86 (0.03, 3.72)	**3.20 (0.10, 6.40)**	**2.66 (0.79, 4.57)**	0.97 (-0.14, 2.08)	1.39 (-0.02, 2.81)	3.25 (0.72, 5.83)	1.06 (-0.96, 3.11)
High	High	P_3N_3 [d]	851	1.82 (1.04, 2.61)	2.13 (0.54, 3.75)	1.33 (-1.37, 4.09)	2.01 (0.42, 3.62)	**2.73 (1.77, 3.71)**	**4.09 (2.84, 5.35)**	**6.85 (4.61, 9.15)**	1.03 (-0.70, 2.79)
Synergy Index (SI)				0.842	0.428	0.832	1.044	**3.272**	**4.560**	**2.418**	-

*: 8df per year for time trend, 6df for current day temperature and mean temperature of previous three days, 3df for relative humidity and mean humidity of previous three days was used in the GAMs. The greatest excess relative risk (ERR%) of the combination with statistical significance for each outcome was in bold. The cutoff points for PM_{10} were 35.80 and 60.88μg/m^3; the cutoff points for NO_2 were 48.06 and 64.41μg/m^3. [a]: This category was regarded as the reference group; [b]: This category was regarded as the individual PM_{10} exposure; [c]: This category was regarded as the individual NO_2 exposure; [d]: This category was regarded as the combined PM_{10} and NO_2 exposure.

We further conducted parametric stratified models to estimate the effects of PM_{10} across three NO_2 levels (Table-18) and the effects of NO_2 across three PM_{10} levels (Table-19). The effects of lag_0 PM_{10} were greatest with statistical significance on the days with high NO_2 level (>64.4μg/m^3) on emergency hospital admissions for CIR, HD and IHD, with an ERR (%) of 0.38 (95% CI: 0.19, 0.56), 0.56 (95% CI: 0.33, 0.80) and 0.83 (95% CI: 0.41, 1.24) respectively (Table-18). However, the effects of lag_0 PM_{10} were greatest with statistical significance on the days with medium NO_2 level (48.1-64.4μg/m^3) on emergency hospital admissions for RES, with an ERR (%) of 0.36 (95% CI: 0.16, 0.56). For COPD admissions, the greatest PM_{10} effect was found on the days with low NO_2 level (<48.1μg/m^3) with an ERR (%) of 1.04 (95% CI: 0.31, 1.77) (Table-18). There was little evidence of NO_2 being a modifier for the effect of PM_{10} on the emergency hospital admissions for asthma, pneumonia and cerebrovascular diseases. Table-19 showed the greatest and statistically significant effects of lag_0 NO_2 on the days with high PM_{10} level (>60.9μg/m^3) on emergency hospital admissions for CIR, HD, IHD and CBD, with an ERR (%) of 0.96 (95% CI: 0.71, 1.20), 1.19 (95% CI: 0.89, 1.50), 1.45 (95% CI: 0.90, 2.00) and 0.59 (95% CI: 0.14, 1.04) respectively. However, the greatest effect of lag_0 NO_2 was found on the days with medium PM_{10} level for RES or on the days with low PM_{10} level for COPD (Table-19). We found little evidence of PM_{10} being a modifier for the effect of NO_2 on the emergency hospital admissions for asthma and pneumonia.

Results suggested NO_2 level modified the effects of PM_{10} and vice versa, which implied some synergistic interactions between particles pollution and nitrogen dioxide on cardiac hospitalizations, and potential antagonistic interactions on total respiratory and COPD hospitalizations.

Table- 18 Effect of current day PM_{10} (ERR% with 95%CI)[&] on the emergency hospital admissions for cardio-respiratory diseases modified by NO_2 levels

Emergency Admissions	NO_2 levels		
	<= 48.06 (n=1216)	**(48.06, 64.41] (n=1220)**	**> 64.41 (n=1216)**
All RES	0.33 (-0.03, 0.69)	**0.36 (0.16, 0.56)**	0.09 (-0.06, 0.24)
COPD	**1.04 (0.31, 1.77)**	0.39 (0.00, 0.78)	0.27 (-0.03, 0.58)
Asthma	0.15 (-1.13, 1.44)	0.00 (-0.67, 0.68)	-0.05 (-0.57, 0.47)
Pneumonia	0.49 (-0.20, 1.20)	0.53 (0.15, 0.92)	0.14 (-0.17, 0.45)
All CIR	-0.01 (-0.45, 0.43)	0.22 (-0.02, 0.46)	**0.38 (0.19, 0.56)**
HD	0.28 (-0.29, 0.85)	0.33 (0.03, 0.63)	**0.56 (0.33, 0.80)**
IHD	0.23 (-0.77, 1.25)	0.30 (-0.24, 0.84)	**0.83 (0.41, 1.24)**
CBD	-0.30 (-1.09, 0.50)	-0.02 (-0.46, 0.42)	-0.04 (-0.38, 0.31)

[&]: 8df per year for time trend, 6df for current day temperature and mean temperature of previous three days, 3df for relative humidity and mean humidity of previous three days was used in the GAMs. Effects were expressed as the percentage increase (ERR (%) with 95% confidence interval) in emergency hospital admissions for circulatory diseases for a 10 $\mu g/m^3$ increment of the current day PM_{10}, across three levels of NO_2. The significantly greatest effect of PM_{10} for each outcome was in bold.

Table- 19 Effect of current day NO_2 (ERR% with 95%CI)[&] on the emergency hospital admissions for cardio-respiratory diseases modified by PM_{10} levels

Emergency Admissions	PM_{10} levels		
	<= 35.80 (n=1216)	**(35.80, 60.88] (n=1220)**	**> 60.88 (n=1216)**
All RES	0.34 (-0.02, 0.71)	**0.45 (0.12, 0.77)**	0.12 (-0.08, 0.31)
COPD	**0.96 (0.20, 1.71)**	0.28 (-0.37, 0.94)	0.62 (0.23, 1.02)
Asthma	0.04 (-1.23, 1.32)	0.74 (-0.38, 1.87)	0.52 (-0.16, 1.20)
Pneumonia	-0.23 (-0.97, 0.51)	0.63 (-0.03, 1.29)	0.07 (-0.34, 0.49)
All CIR	0.54 (0.09, 0.99)	0.43 (0.03, 0.84)	**0.96 (0.71, 1.20)**
HD	0.70 (0.12, 1.28)	0.70 (0.19, 1.22)	**1.19 (0.89, 1.50)**
IHD	0.74 (-0.28, 1.77)	0.65 (-0.26, 1.57)	**1.45 (0.90, 2.00)**
CBD	0.23 (-0.59, 1.05)	-0.02 (-0.75, 0.72)	**0.59 (0.14, 1.04)**

[&]: 8df per year for time trend, 6df for current day temperature and mean temperature of previous three days, 3df for relative humidity and mean humidity of previous three days was used in the GAMs. Effects were expressed as the percentage increase (ERR (%) with 95% confidence interval) in emergency hospital admissions for circulatory diseases for a 10 $\mu g/m^3$ increment of the current day NO_2, across three levels of PM_{10}. The significantly greatest effect of NO_2 for each outcome was in bold.

4.3.5 Joint effects/Interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations

We fitted the bivariate response surface models to display the joint effects of PM_{10} and ozone on emergency cardio-respiratory admissions (Figure-19), using current day pollutants concentrations as continuous variables. The results showed that the joint effect patterns of PM_{10} and ozone were very similar on CIR, HD and IHD, less so for CBD, RES and COPD, and displayed another similar pattern for asthma and pneumonia. Response surfaces showed some interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations.

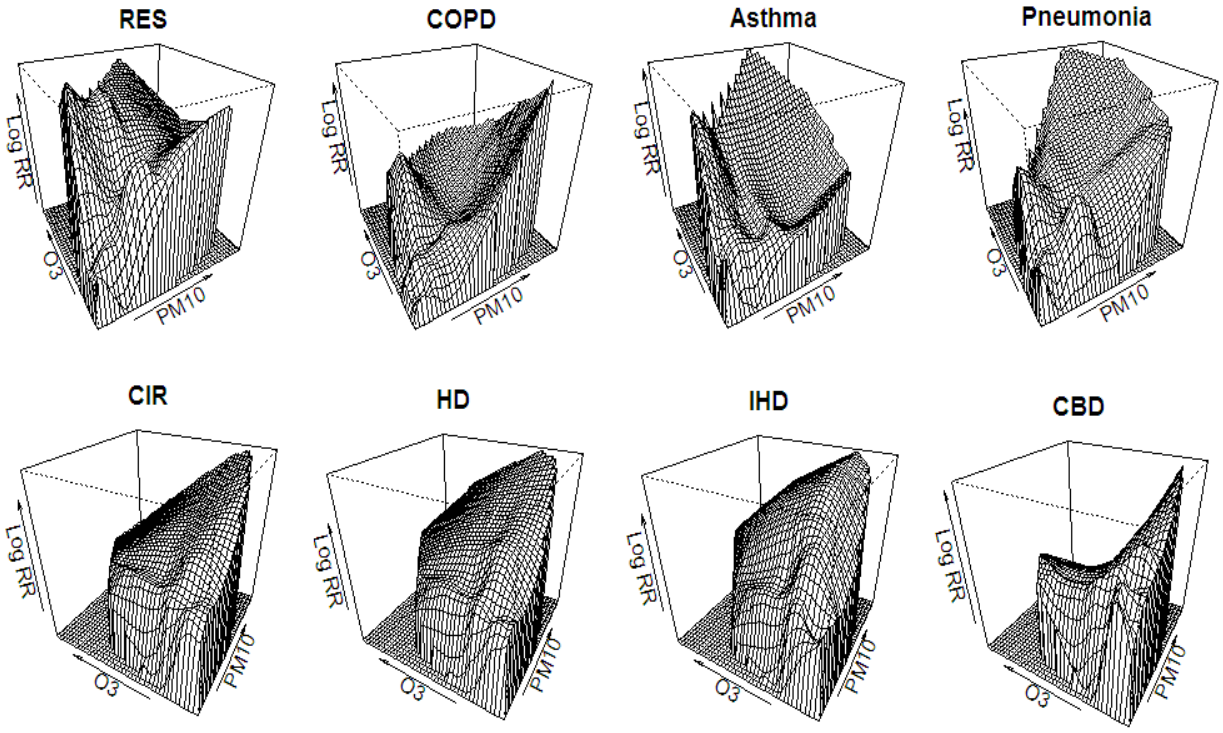

Figure- 18 Bivariate Response Surfaces of Current Day PM_{10} and Ozone on Emergency Cardio-respiratory Hospital Admissions

POlevel was created to denote the different combinations of current day (lag_0) PM_{10} and O_3 levels and was used to explore the joint effects of particles and ozone pollution as a mixture, setting the combination of low levels of PM_{10} and O_3 as the reference group. For emergency hospital admissions for all studied subgroups of cardio-respiratory diseases, the greatest effects of particles pollution and ozone mixture were not in the combination that PM_{10} and ozone concentrations were both in the high levels (Table-20). The greatest ERRs% were found in low level's PM_{10} combined with high level's O_3 for emergency hospital admissions for RES and pneumonia, and in high level's PM_{10} combined with low level's O_3 for CIR, CBD, and COPD. The combination of both medium levels of PM_{10} and O_3 showed the greatest effect for emergency hospital admissions for asthma, and high PM_{10} concentration joined with medium O_3 exposure showed the greatest effects for cardiac diseases and IHD. The synergy indices (SI) for these categories of cardio-respiratory outcomes were all less than 1 except that of IHD. Results showed there might be some potential antagonistic interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations.

Table- 20 The Joint Effects of PM_{10} and Ozone (ERR% with 95%CI)[*] on the Emergency Hospital Admissions for Cardio-respiratory Diseases

PM_{10}	O_3	PO level	No.of Days	RES	COPD	Asthma	Pneumonia	CIR	HD	IHD	CBD
Low	Low	P_1O_1 [a]	769	0	0	0	0	0	0	0	0
Medium	Low	P_2O_1	314	0.47 (-0.42, 1.38)	1.82 (-0.03, 3.70)	1.51 (-1.65, 4.77)	-0.61 (-2.41, 1.22)	-0.03 (-1.14, 1.09)	-0.86 (-2.26, 0.56)	-0.56 (-3.06, 1.99)	1.00 (-1.04, 3.09)
High	Low	P_3O_1 [b]	133	2.84 (1.56, 4.13)	**4.55 (1.98, 7.18)**	2.73 (-1.54, 7.19)	1.07 (-1.50, 3.70)	**2.87 (1.31, 4.47)**	2.22 (0.26, 4.21)	3.04 (-0.50, 6.71)	**4.18 (1.25, 7.20)**
Low	Medium	P_1O_2	399	0.59 (-0.22, 1.40)	2.10 (0.39, 3.84)	1.67 (-1.23, 4.65)	-0.38 (-2.04, 1.31)	-0.98 (-1.97, 0.03)	-1.77 (-3.04, -0.48)	-0.67 (-2.92, 1.62)	0.02 (-1.79, 1.86)
Medium	Medium	P_2O_2	502	1.07 (0.29, 1.86)	2.19 (0.56, 3.85)	**3.31 (0.55, 6.14)**	1.59 (-0.05, 3.25)	0.16 (-0.80, 1.14)	-0.22 (-1.43, 1.02)	2.52 (0.32, 4.77)	0.97 (-0.80, 2.76)
High	Medium	P_3O_2	318	2.83 (1.83, 3.83)	3.84 (1.83, 5.90)	-0.30 (-3.58, 3.09)	3.50 (1.43, 5.60)	2.66 (1.45, 3.89)	**2.89 (1.35, 4.45)**	**5.16 (2.37, 8.03)**	1.98 (-0.25, 4.26)
Low	High	P_1O_3 [c]	48	**3.85 (1.91, 5.83)**	1.97 (-2.02, 6.12)	1.33 (-5.22, 8.33)	**7.22 (3.16, 11.43)**	-0.50 (-2.89, 1.95)	-0.34 (-3.39, 2.82)	-1.41 (-6.74, 4.23)	-0.23 (-4.49, 4.21)
Medium	High	P_2O_3	404	2.55 (1.69, 3.42)	2.92 (1.13, 4.73)	3.08 (0.08, 6.17)	3.08 (1.29, 4.90)	-0.10 (-1.14, 0.96)	-0.68 (-2.01, 0.66)	1.01 (-1.36, 3.45)	1.13 (-0.78, 3.08)
High	High	P_3O_3 [d]	765	2.21 (1.38, 3.05)	2.45 (0.75, 4.17)	2.89 (-0.01, 5.87)	2.96 (1.29, 4.66)	0.56 (-0.44, 1.57)	1.34 (0.06, 2.64)	3.95 (1.64, 6.32)	-0.56(-2.37,0.27)
Synergy Index (SI)				0.331	0.376	0.711	0.358	0.237	0.713	2.422	0.143

*: The combination of low level's PM_{10} and O_3 was used as the reference group, and the greatest excess relative risk (ERR%) of the combination for each emergency admission outcome was in bold. The cutoff points for PM_{10} were 35.80 and 60.88 μg/m^3; the cutoff points for O_3 were 24.45 and 46.81 μg/m^3. [a]: This category was regarded as the reference group; [b]: This category was regarded as the individual PM_{10} exposure; [c]: This category was regarded as the individual O_3 exposure; [d]: This category was regarded as the combined PM_{10} and O_3 exposure.

Further parametric stratification models were conducted to estimate the effects of PM_{10} modified by ozone level (Table-21) and the effects of ozone modified by PM_{10} level (Table-22). The effects of current day PM_{10} were greatest during the days with low ozone level (<=24.5μg/m^3) on emergency hospitalizations for RES, COPD, and CBD. At the same time, the greatest effects of current day PM_{10} were found during the days with medium ozone level (24.5 ~ 46.8μg/m^3) on emergency hospitalizations for CIR, HD, IHD and pneumonia. The differences of PM_{10} effects across ozone levels were all statistically significant. Results (Table-21) suggested that the effects of PM_{10} were modified by ozone level and there might be some antagonistic interactions between particles pollution and ozone on cardio-respiratory hospitalizations.

Table- 21 Effect of Current day PM_{10} (ERR% with 95%CI)[&] modified by O_3 level

Emergency Admissions	O_3 levels		
	<= 24.45 (n=1216)	**(24.45, 46.81] (n=1219)**	**> 46.81 (n=1217)**
All RES	**0.42 (0.22, 0.61)**[‡]	**0.38 (0.20, 0.56)**[‡]	-0.03 (-0.17, 0.12)
COPD	**0.93 (0.54, 1.32)**[‡]	0.39 (0.03, 0.76)	0.06 (-0.24, 0.37)
Asthma	0.50 (-0.18, 1.18)	-0.44 (-1.06, 0.18)	-0.03 (-0.55, 0.50)
Pneumonia	0.19 (-0.21, 0.59)	**0.73 (0.34, 1.12)**[‡]	0.03 (-0.27, 0.33)
All CIR	0.50 (0.26, 0.74)	**0.89 (0.66, 1.11)**[‡]	0.21 (0.03, 0.40)
HD	0.44 (0.14, 0.75)	**1.09 (0.81, 1.38)**[‡]	0.48 (0.25, 0.72)
IHD	0.45 (-0.10, 1.01)	**1.35 (0.84, 1.86)**	0.88 (0.47, 1.30)
CBD	**0.53 (0.08, 0.99)**[‡]	**0.46 (0.05, 0.88)**[‡]	-0.34 (-0.68, 0.00)

[&]: Effects were expressed as the percentage increase (ERR (%) with 95% confidence interval) in emergency hospital admissions for cardio-respiratory diseases for a 10 μg/m^3 increment of current day PM_{10}, across three levels of O_3. Compared with PM_{10} effects at high ozone level, [†]:$p<0.05$; [‡]:$p<0.01$. The significantly greatest effect of PM_{10} on each outcome was in bold.

Table-22 showed that the greatest effects of lag_0 ozone exposure were found during the days with the medium PM_{10} level (35.8 ~ 60.9μg/m^3) on emergency hospital admissions for RES, and COPD, and the differences of ozone effect across three PM_{10} levels were statistically significant. The greatest effects of lag_0 ozone were also found in the medium or low level of PM_{10} for emergency hospital admissions for pneumonia and asthma, but the differences of ozone effects across three PM_{10} levels were not statistically significant. There was little evidence for PM_{10} being a modifier for the effects of lag_0 ozone on emergency hospital admissions for total circulatory diseases and its three subsets.

Table- 22 Effect of current day ozone (ERR% with 95%CI)[&] modified by PM_{10} levels

Emergency Admissions	PM_{10} levels		
	<= 35.80 (n=1216)	**(35.80, 60.88] (n=1220)**	**>= 60.88 (n=1216)**
All RES	0.48 (0.14, 0.82) [†]	**0.53 (0.32, 0.74)** [‡]	0.09 (-0.06, 0.25)
COPD	0.44 (-0.27, 1.15)	**0.55 (0.13, 0.98)** [†]	-0.03 (-0.34, 0.29)
Asthma	0.85 (-0.36, 2.07)	0.94 (0.21, 1.69)	0.54 (-0.01, 1.08)
Pneumonia	0.80 (0.11, 1.49)	0.50 (0.07, 0.92)	0.36 (0.06, 0.67)
All CIR	-0.40 (-0.83, 0.02)	0.00 (-0.26, 0.26)	-0.39 (-0.58, -0.20)
HD	-0.45 (-0.99, 0.10)	0.00 (-0.33, 0.33)	-0.18 (-0.43, 0.06)
IHD	-0.47 (-1.43, 0.50)	0.11 (-0.48, 0.70)	-0.06 (-0.49, 0.37)
CBD	-0.33 (-1.10, 0.44)	0.04 (-0.43, 0.51)	-0.65 (-1.00, -0.31)

[&]: Effects were expressed as the percentage increase (ERR (%) with 95% confidence interval) in emergency hospital admissions for cardio-respiratory diseases for a 10 μg/m^3 increment of lag_0 day O_3, across three levels of PM_{10}. Compared with ozone effects at high PM_{10} level, [†]:$p<0.05$; [‡]:$p<0.01$. The significantly greatest effect of ozone for each outcome was in bold.

4.3.6 Joint effects/Interactions between PM_{10} and SO_2 on cardio-respiratory hospitalizations

We fitted the bivariate response surface model to display the joint effects of current day (lag_0) PM_{10} and SO_2 on emergency hospital admissions for cardio-respiratory diseases using pollution concentrations as continuous variables, to explore the potential interactions between PM_{10} and SO_2 (Figure-20). Results showed that the joint effect patterns of PM_{10} and SO_2 were similar on emergency hospital admissions for RES, COPD and pneumonia; and they were also very similar on emergency hospital admissions for CIR, HD, and IHD, but different from that of CBD and asthma. However, the joint effects between PM_{10} and SO_2 did not show any clear patterns to be interpreted.

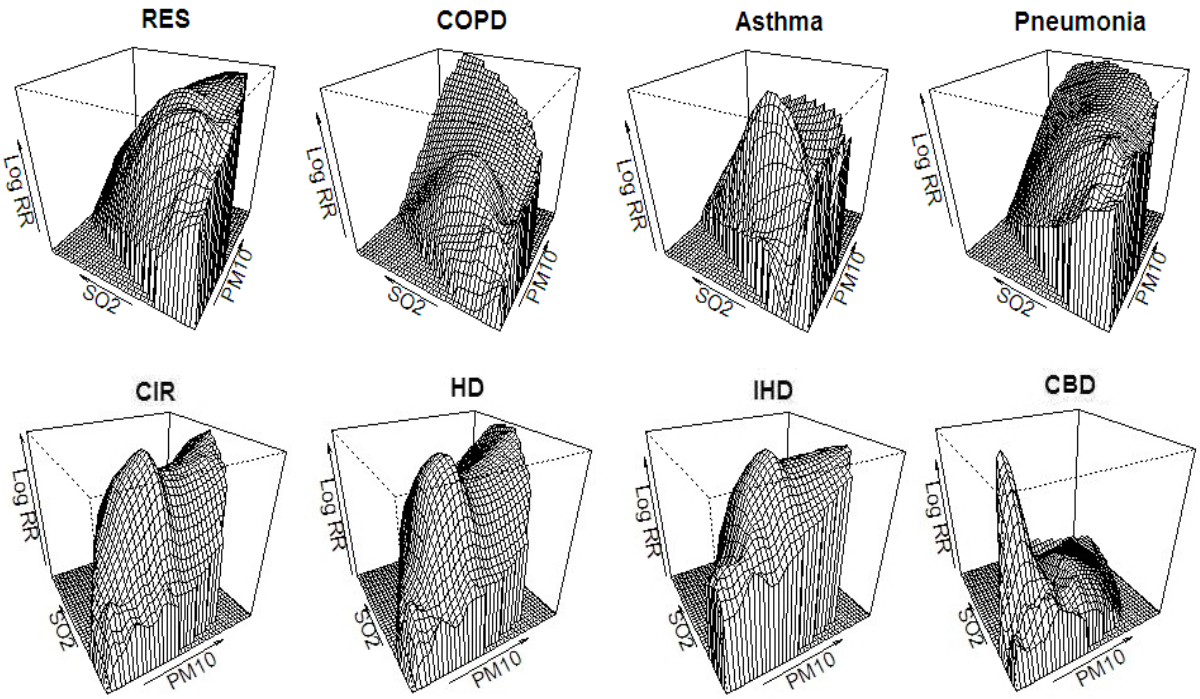

Figure- 20 Bivariate Response Surfaces of Current Day PM_{10} and SO_2 on Emergency Ccardio-Respiratory Hospital Admissions

We created *PSlevel* to denote the different combinations of current day (lag_0) PM_{10} and SO_2 levels and used the joint effect models to explore the joint effects of particles pollution and sulfur dioxide as a mixture, setting the combination of low levels of PM_{10} and SO_2 as the reference group. We found the greatest and statistically significant joint effects in the combination when PM_{10} and SO_2 concentrations were both in the high levels on emergency hospital admissions for CIR, HD and IHD (ERR%=3.68, 5.33 and 7.48, respectively), but not for CBD (Table-23). The synergy indices (SI) for these three categories of circulatory outcomes were 1.76, 1.66 and 2.07, respectively. Results showed there might be some synergism between PM_{10} and SO_2 for cardiac hospitalizations, especially for IHD hospital admissions. However, the greatest ERRs% for respiratory outcomes showed some inconsistencies, which were found on the days when low SO_2 concentrations combined with high PM_{10} for COPD with the synergy index (SI) 0.54. Results showed the potential antagonism between PM_{10} and SO_2 on COPD hospitalizations.

Table- 23 The Joint Effects of Particles Pollution and Sulfur Dioxide (ERR% with 95%CI)[*] on the Emergency Hospital Admissions for Cardio-respiratory Diseases

PM_{10}	SO_2	PSlevel	No.of Days	RES	COPD	Asthma	Pneumonia	CIR	HD	IHD	CBD
Low	Low	P_1S_1 [a]	522	0	0	0	0	0	0	0	0
Medium	Low	P_2S_1	499	0.51 (-0.33, 1.35)	0.97 (-0.76, 2.73)	-0.54 (-3.32, 2.32)	0.81 (-0.97, 2.63)	0.30 (-0.74, 1.36)	0.00 (-1.33, 1.35)	1.15 (-1.21, 3.57)	0.82 (-1.08, 2.76)
High	Low	P_3S_1 [b]	192	**1.87 (0.74, 3.01)**	**3.74 (1.41, 6.14)**	-1.45 (-5.06, 2.29)	1.86 (-0.58, 4.37)	0.96 (-0.44, 2.39)	1.37 (-0.42, 3.19)	2.08 (-1.10, 5.36)	0.54 (-2.02, 3.16)
Low	Medium	P_1S_2	354	-0.48 (-1.39, 0.43)	-0.49 (-2.38, 1.43)	-5.46 (-8.49, -2.33)	-0.26 (-2.13, 1.65)	1.07 (-0.07, 2.24)	1.03 (-0.44, 2.52)	1.54 (-1.04, 4.19)	1.00 (-1.06, 3.10)
Medium	Medium	P_2S_2	425	0.58 (-0.32, 1.49)	0.98 (-0.87, 2.86)	-0.47 (-3.50, 2.66)	0.73 (-1.15, 2.64)	1.01 (-0.12, 2.14)	0.53 (-0.89, 1.97)	3.15 (0.59, 5.79)	1.63 (-0.42, 3.72)
High	Medium	P_3S_2	444	1.16 (0.18, 2.15)	0.33 (-1.63, 2.34)	-2.11 (-5.29, 1.19)	1.27 (-0.74, 3.31)	1.46 (0.25, 2.68)	1.57 (0.04, 3.12)	3.68 (0.92, 6.52)	0.93 (-1.26, 3.17)
Low	High	P_1S_3 [c]	340	-0.65 (-1.59, 0.30)	0.04 (-1.93, 2.06)	-4.42 (-7.64, -1.08)	-0.17 (-2.09, 1.78)	1.13 (-0.07, 2.34)	1.84 (0.30, 3.40)	1.53 (-1.15, 4.29)	-0.45 (-2.57, 1.71)
Medium	High	P_2S_3	296	0.40 (-0.56, 1.37)	1.50 (-0.50, 3.53)	-0.52 (-3.87, 2.95)	0.68 (-1.29, 2.68)	1.46 (0.25, 2.69)	1.81 (0.26, 3.38)	2.17 (-0.57, 4.99)	1.05 (-1.13, 3.28)
High	High	P_3S_3 [d]	580	1.43 (0.50, 2.37)	2.06 (0.15, 4.01)	-1.05(-4.17,2.18)	**2.20 (0.26, 4.17)**	**3.68 (2.50, 4.87)**	**5.33 (3.81, 6.87)**	**7.48(4.75, 10.28)**	1.27 (-0.82, 3.41)
Synergy Index (SI)				1.176	0.544	-	1.297	1.758	1.661	2.070	-

*: 8df per year for time trend, 6df for current day temperature and mean temperature of previous three days, 3df for relative humidity and mean humidity of previous three days was used in the GAMs. The statistically significant greatest excess relative risk (ERR%) of the combination for each outcome was in bold. The cutoff points for PM_{10} were 35.80 and 60.88 $\mu g/m^3$; the cutoff points for SO_2 were 12.79 and 20.87 $\mu g/m^3$. [a]: This category was regarded as the reference group; [b]: This category was regarded as the individual PM_{10} exposure; [c]: This category was regarded as the individual SO_2 exposure; [d]: This category was regarded as the combined PM_{10} and SO_2 exposure.

We conducted further parametric stratified models to estimate the effects of PM_{10} across three SO_2 levels (Table-24) and the effects of SO_2 across three PM_{10} levels (Table-25). The effect of lag_0 PM_{10} was greatest with statistical significance during the days with high SO_2 level (>20.9μg/m^3) on emergency hospital admissions for CIR, HD and IHD, with an ERR (%) of 0.41% (95% CI: 0.25-0.56%), 0.64% (95% CI: 0.44-0.84%) and 0.91% (95% CI: 0.55-1.26%) respectively (Table-24). Results suggested SO_2 level modified the effects of PM_{10}, which implied some synergistic interactions between particles pollution and sulfur dioxide on cardiac hospitalizations. The effect of lag_0 PM_{10} was greatest with statistical significance during the days with low SO_2 level (<12.8μg/m^3) on emergency COPD hospital admissions with an ERR (%) of 0.67% (95% CI: 0.23-1.11%) (Table-24). However, there was little evidence of SO_2 being a modifier for the effects of lag_0 PM_{10} on emergency hospital admissions for RES, asthma and pneumonia. Table-25 showed the effects of lag_0 SO_2 across three PM_{10} levels on emergency hospital admissions for respiratory and circulatory diseases, respectively. There was also little evidence of PM_{10} being the modifier for the effects of SO_2 on the cardio-respiratory diseases outcomes.

Table- 24 Effect of current day PM_{10} (ERR% with 95%CI)[&] on the emergency hospital admissions for circulatory diseases modified by SO_2 levels

Emergency Admissions	SO_2 levels		
	<= 12.79 (n=1213)	**(12.79, 20.87] (n=1223)**	**> 20.87 (n=1216)**
All RES	0.29 (0.08, 0.50)	0.30 (0.13, 0.46)	0.23 (0.10, 0.36)
COPD	**0.67 (0.23, 1.11)**	0.20 (-0.14, 0.54)	0.33 (0.07, 0.59)
Asthma	-0.55 (-1.26, 0.17)	0.41 (-0.16, 0.98)	0.20 (-0.26, 0.67)
Pneumonia	0.36 (-0.09, 0.82)	0.35 (0.02, 0.69)	0.32 (0.07, 0.58)
All CIR	0.16 (-0.11, 0.43)	0.11 (-0.09, 0.31)	**0.41 (0.25, 0.56)** [†]
HD	0.30 (-0.04, 0.64)	0.23 (-0.03, 0.49)	**0.64 (0.44, 0.84)** [†]
IHD	0.44 (-0.16, 1.05)	0.48 (0.02, 0.95)	**0.91 (0.55, 1.26)**
CBD	0.03 (-0.46, 0.52)	-0.11 (-0.48, 0.26)	0.06 (-0.23, 0.35)

[&]: 8df per year for time trend, 6df for current day temperature and mean temperature of previous three days, 3df for relative humidity and mean humidity of previous three days was used in the GAMs. Effects were expressed as the percentage increase (ERR (%) with 95% confidence interval) in emergency hospital admissions for circulatory diseases for a 10 $\mu g/m^3$ increment of current day PM_{10}, across three levels of SO_2. The significantly greatest effect of PM_{10} for each outcome was in bold; [†]：Compared with the PM_{10} effects during days with medium SO_2 level, $P<0.05$.

Table- 25 Effect of current day SO_2 (ERR% with 95%CI)[&] on the emergency hospital admissions for circulatory diseases modified by PM_{10} levels

Emergency Admissions	PM_{10} levels		
	<= 35.80 (n=1216)	(35.80, 60.88] (n=1220)	> 60.88 (n=1216)
All RES	-0.35 (-0.83, 0.13)	-0.20 (-0.59, 0.19)	-0.06 (-0.29, 0.16)
COPD	0.25 (-0.75, 1.26)	0.16 (-0.64, 0.96)	0.31 (-0.13, 0.76)
Asthma	-2.09 (-3.78, -0.38)	-0.46 (-1.84, 0.93)	0.27 (-0.53, 1.08)
Pneumonia	-0.83 (-1.78, 0.13)	-0.37 (-1.16, 0.42)	-0.04 (-0.46, 0.40)
All CIR	0.55 (-0.05, 1.15)	0.42 (-0.07, 0.90)	0.55 (0.28, 0.81)
HD	0.97 (0.20, 1.75)	0.47 (-0.15, 1.09)	0.81 (0.47, 1.15)
IHD	1.03 (-0.32, 2.39)	0.45 (-0.64, 1.55)	0.48 (-0.12, 1.08)
CBD	-0.28 (-1.35, 0.80)	0.23 (-0.64, 1.12)	0.12 (-0.37, 0.61)

[&]: 8df per year for time trend, 6df for current day temperature and mean temperature of previous three days, 3df for relative humidity and mean humidity of previous three days was used in the GAMs. Effects were expressed as the percentage increase (ERR (%) with 95% confidence interval) in emergency hospital admissions for circulatory diseases for a 10 $\mu g/m^3$ increment of current day SO_2, and the differences of SO_2 effects across three levels of PM_{10} were statistically non-significant.

4.4 Discussion

4.4.1 Main findings

We confirmed the associations between ambient pollution and emergency hospital admissions for cardio-respiratory diseases in single-pollutant models in Hong Kong. We used three parallel time series approaches to examine the interaction between particulate matter and gaseous pollutants. We found synergistic interactions between PM_{10} and NO_2 or SO_2 on emergency cardiac hospitalizations. We also found antagonistic interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations, and possible antagonistic interactions between PM_{10} and NO_2 on COPD admissions as well.

4.4.1.1 Effect estimates compared with previous Hong Kong studies

We detected the statistically significant associations between air pollution and respiratory hospitalizations in single pollutant model, especially for COPD. We also detected the statistically significant associations between air pollution and circulatory hospitalizations, especially for IHD. Our results are consistent with those reported in previous Hong Kong studies examining the effects of pollution on hospital admissions for cardio-respiratory diseases (Lee et al. 2006; Ko et al. 2007a, 2007b; Wong CM et al. 1999, 2002; Wong GWK et al. 2001; Wong TW et al. 1999). However, in general, the effect estimates for each pollutant detected in our study were smaller in size compare with those in previous Hong Kong studies. The differences might be attributable to some several reasons. First of all, we estimated the single-day lag effects in this study which were necessary for examining the joint effects, while the estimated effects of multiday average concentrations of pollutants were always greater in magnitude than estimated effects of single day lags in most

cases. Secondly, we used more conservative scenarios in model specifications and *df* choosing to adjust for the confounding effects from weather factors such as temperature and relative humidity, which might also lead to lower effect estimates of air pollution. For example, we added two terms of temperature (mean temperature of current day, $Temp_0$, and previous 3 days' moving average, $Temp_{1-3}$) and two terms of relative humidity (mean humidity of current day, $Humidity_0$, and previous 3 days' moving average, $Humid_{1-3}$) into the core model. We also chose higher number of *df* (a *df* of 6) for temperature than that for humidity (a *df* of 3) in order to capture the well-known "J-shape" nonlinear relationship between temperature and morbidity (Bell et al. 2005; Peng et al. 2006, 2008).

4.4.1.2 Interactions between particulate matter and gaseous pollutants

In this study, we used three parallel time series approaches (bivariate surface model, joint effect model and parametric stratified model) to examine the possible interactions between PM_{10} and gaseous pollutants on the emergency cardio-respiratory hospitalizations.

4.4.1.2.1 Interactions between PM_{10} and NO_2 on cardiac hospitalizations

Results showed that the joint effects patterns for PM_{10} and NO_2 were similar on emergency hospital admissions for CIR and its subsets (Figure-18), and the greatest joint effects were the mixture when PM_{10} and NO_2 concentrations were both at high levels (Table-17). NO_2 modified the effects of PM_{10} on emergency hospital admissions for cardiac diseases, and vice versa (Table-18,19). Three parallel approaches produced consistent results and supported synergy between PM_{10} and NO_2 on emergency cardiac hospitalizations.

The bivariate response surface approach is flexible for examining interactive effects between two continuous predictors on the dependent variable without a rigid linear assumption and has been used in several previous air pollution studies (Ren et al. 2006; Roberts 2004). We used it to show the pattern of joint effect graphically. However, it cannot provide the parametric estimates and so makes it difficult to judge whether effect modification has occurred or not. Another two approaches (the joint effect model and parametric stratified model) would provide the quantitative estimates and we used them to estimate the joint effects of PM_{10} and NO_2 parametrically and the modified effects of one pollutant on the other.

Synergy is defined as occurring if the effect of the combined exposure is greater than the sum of the effects of two or more individual components in the mixture. It is necessary to have estimates on both the individual and the combined effects to evaluate the presence of the synergism (Mauderly and Samet 2009; Rothman KJ et al. 2008). Sometimes synergy is used loosely and considered as the case where none of the mixture components has an effect when given alone, but exposure to the mixture produces some response (Schlesinger 1995). The real-world conditions in environmental epidemiological studies make it very complex to estimate the effects of several pollutants separately and in combination simultaneously. We resorted to joint effect model that had been commonly used in traditional epidemiological studies (Tse et al. 2011; Wang et al. 2009) by dividing the pollutant concentrations into three categories and creating a new categorical variable *PNlevel* to denote the nine different combinations of PM_{10} and NO_2 as a mixture. Using the combination of two pollutants both at low levels as the relative non-exposed (reference) group, we estimated the effect of the combination of two pollutants both at high levels as the joint effect of the combined exposure. At the same time, we estimated the effects of

combinations of one pollutant at high level and another pollutant at low level as the effects of the individual exposures. So we could estimate whether synergy occurred or not by calculating the synergy index, which was defined as the ERR of the combined exposure group divided by the sum of the ERRs of the individual exposure groups. We found no significant effects of individual exposures but much greater and statistically significant effects of combined exposure, and the synergy indices on emergency hospital admissions for CIR, HD and IHD were much higher than 1 (Table 17), which suggested some synergistic interactions between PM_{10} and NO_2 for cardiac hospitalizations. Further analysis using parametric stratified model evaluated the modified effects of NO_2 on PM_{10} (Table 18) and the modified effects of PM_{10} on NO_2 (Table 19). The effects of PM_{10} were greater during the days with high NO_2 level and the effects of NO_2 were also greater during the days with high PM_{10} level, providing further evidence of the synergy between PM_{10} and NO_2 on emergency hospital admissions for cardiac diseases.

Many epidemiological studies confirmed the adverse effects of PM_{10} or NO_2 on mortality and morbidity, however, the effect of a single pollutant could sometimes be seen as a proxy for another air pollutant or for a mixture of air pollutants. It is not always possible to identify, in the presence of several pollutants in a complex atmosphere, whether an interaction is present, and, if so, the exact type of interaction. Exposure to gases and particles mixtures may result in respiratory tract or cardiovascular responses which are simply additive, or reflect synergistic or antagonistic interactions (Schlesinger 1995). Few epidemiological studies examined the interaction between PM_{10} and NO_2 and the evidence so far is inadequate and controversial (Hong et al. 2002; Ponka et al. 1998; Simpson et al. 1997; Sunyer and Basagana 2001; Wong TW et al. 1999). A study in Seoul examined the interaction

between particulates and gaseous pollutants (Hong et al. 2002). Authors reported the ERR for each interquartile range in NO_2 increased from 2.8% to 3.2% when PM_{10} concentrations were changed from below to above the median level (67.6 $\mu g/m^3$) in the model. At the same time, the ERR for PM_{10} decreased from 4.8% to -1.5% when NO_2 concentrations were changed from below to above the median level (59.0 $\mu g/m^3$). Authors drew the conclusion that PM_{10} and gaseous pollutants were interactive with respect to their effects on the risk of stroke mortality, but the direction of the interaction (effect modification) seemed to be inconsistent in that study. A previous Hong Kong study detected some significant positive interactions between NO_2, O_3, and PM_{10} on hospital admissions for cardio-respiratory diseases (Wong TW et al. 1999). The authors explored interactions between pollutants using pairwise analyses by entering two pollutants and their interaction term into the model. Each pollutant was analyzed as a continuous variable with the other pollutant as a dichotomous variable using the median as the cutoff point, which was similar to the approach we used in the parametric stratified model. However the authors did not show different effects of one pollutant across the high/low levels of the other pollutant. Another study reported no interactions between particles and gaseous pollutants on mortality in patients with COPD, based on the absence of statistical significance for the product terms (both pollutants as continuous variables and all interaction terms had a P-value > 0.5) (Sunyer and Basagana 2001). There was also no evidence of interactions between PM and gaseous pollutants on daily mortality in Brisbane, Australia (Simpson et al. 1997). In the above mentioned studies that examined the joint effects between PM_{10} and NO_2, results were inconsistent and inclusive, and the statistical approaches and power might not be adequate.

In the studies of Air Pollution and Health: A European Approach 2 (APHEA2), researchers examined the short-term effects of ambient particles on total mortality in 29 European cities with emphasis on effect modification (Aga et al. 2003; Katsouyanni et al. 2001). Authors identified that long term NO_2 concentration as the most important effect modifier: the effect of an increase of 10 $\mu g/m^3$ in PM_{10} ranges from 0.19% (95% CI = 0.00-0.41%) in cities with low long-term average NO_2 (about 40$\mu g/m^3$) to 0.80% (95% CI = 0.67-0.93%) in cities with high long-term average NO_2 (about 70$\mu g/m^3$). These studies supported our findings about the synergistic interactions between PM_{10} and NO_2 in another way. The later APHENA study (Air Pollution and Health: A Combined European and North American Approach) demonstrated that the effect modification by other pollutants differed in Europe and the United States: higher levels of NO_2 and a larger NO_2:PM_{10} ratio were associated with a greater PM_{10} effect on mortality in Europe; this pattern was also present in the United States but was less pronounced (Katsouyanni et al. 2009; Samoli et al. 2008).

The underlying mechanisms linking air pollutants to increased cardiovascular risk have been studied. An investigation showed that both PM_{10} and NO_2 were associated with changes in the global coagulation function and suggested a tendency towards hypercoagulability after short-term exposure to air pollution, which might contribute to trigger cardiovascular events (Baccarelli et al. 2007). Some other researchers suggested that higher PM_{10} or NO_2 concentrations are associated with lower cardiac autonomic control, and highlighted a putative mechanism through which air pollution is associated with cardiovascular diseases (Liao et al. 2004). Nemmar et al. even found that the smallest particles could translocate from the lungs into the circulation and thus influence cardiovascular endpoints more directly (Nemmar et al. 2002). However, the mechanisms underlying specific interaction between PM_{10} and NO_2 are

not very clear. An early animal study examined the mechanism of physical adsorption hypothesis and suggested the particles served as carriers for nitrogen dioxide, delivering this irritant gas to localized areas within the lungs where the particles deposited (Boren 1964). This was an early example of synergism. We used the same lag_0 exposure of PM_{10} and NO_2 to examine the interaction, mechanisms through the chemical reaction in the exposure atmosphere or on a particle surface, or through the alteration of the pulmonary environment were also suggested to explain the interaction between particle and gaseous pollutants (Schlesinger 1995). A recent experimental study in patients with stable coronary heart disease and impaired left ventricular systolic function found the lack of effect of NO_2 exposure alone on heart rate variability and further supported our findings on the synergism (Scaife et al. 2012). Experimental studies found that combination of NO_2 with respirable acidic aerosols would demonstrate interactive effects on rat lungs (Last and Warren 1987).

However, results on the joint effects between PM_{10} and NO_2 on respiratory hospitalizations were inconsistent with those on circulatory diseases. The synergy index on COPD was less than 1, with a value of 0.43. NO_2 level modified the effects of PM_{10} on COPD hospitalization, showing the greatest PM_{10} effect on the days with low NO_2 level. PM_{10} level also modified the effects of NO_2 on COPD hospitalization, showing the greatest NO_2 effect on the days with low PM_{10} level. Results suggested the potential antagonism between PM_{10} and NO_2 on COPD hospital admissions. The underlying mechanisms linking this antagonistic interaction were still unknown. Further epidemiological studies are needed to be conducted in other settings to check whether these conflicting results were chance occurrences. Experimental studies are also needed to test the interactions between PM_{10} and NO_2 at low concentrations similar to environmental exposures to explore the possible mechanisms.

4.4.1.2.2 Interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations

Results showed that the greatest joint effects of PM_{10} and O_3 on cardio-respiratory hospitalizations were not in the category when PM_{10} and O_3 were both at high levels (Figure-19, Table-20). Ozone modified the effects of PM_{10} on almost all subsets of emergency cardio-respiratory hospital admissions with statistical significance except asthma (Table-21). Evidences of PM_{10} being a modifier of the effects of ozone were found on emergency hospitalizations for total respiratory diseases and COPD, but not on the circulatory endpoints (Table-22). Three parallel approaches produced similar results about the antagonistic interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations.

We used emergency hospital admissions from all and several dominant causes of cardio-respiratory diseases as health outcomes to examine the consistency of the findings. In general, results were consistent except when we examined the effects of O_3 across the different levels of PM_{10}. PM_{10} modified the O_3 effects on all respiratory, and COPD admissions, but not on the circulatory outcomes and three subsets. The main reason for this phenomenon might be attributed to that we chose a priori exposure at lag_0 for ozone but the overall effects of lag_0 ozone on emergency hospital admissions for circulatory diseases and its subsets were statistically nonsignificant in single-pollutant models.

Several epidemiological studies examined the interactions between PM_{10} and O_3 but the evidences are quite inadequate and controversial. Some researchers reported harmful interaction at high concentrations (higher than 90^{th} or 95^{th} percentiles) of PM_{10} and O_3. A study in Moscow, Russia found on the days with O_3 concentrations above the 90^{th} percentile ($41\mu g/m^3$), PM_{10} risk for all-cause mortality was threefold

greater and for cerebrovascular disease mortality was fourfold greater (Revich and Shaposhnikov 2010). A study in Shanghai, China found PM_{10} concentrations above 95th percentile (225.7μg/m^3) would significantly increased the effect of O_3 on total mortality (Chen et al. 2007). Another study in Helsinki, Finland found high concentrations of PM_{10}, ozone, and nitrogen dioxide had a further harmful additive effect on mortality (Ponka et al. 1998): concentration of O_3 increased the influence of PM_{10}, NO_2, and SO_2, especially when the O_3 concentration was high (i.e., >42μg/m^3, 90th percentile). A study using median as cut-off point found no significant effect of PM_{10} during the days when O_3 levels were below the median (116.7ppb, 228.7μg/m^3), while a significant effect of PM_{10} was found on days when O_3 concentrations exceeded the median, suggesting a synergic effect of PM_{10} and O_3 on respiratory mortality on days when ambient O_3 levels are high (Tellez-Rojo et al. 2000). However, a study conducted in Brisbane, Australia accounted for interaction effect by introduction of a dummy day variable for "low" and "high" value of gaseous pollutants ("high" value for the highest 10% of the data), and found no apparent interactions between particulates and gaseous pollutants on mortality (Simpson et al. 1997). Sunyer et al. also reported no interaction between particles and gaseous pollutants in Barcelona because all interaction terms had a P-value larger than 0.5 (Sunyer and Basagana 2001). All these studies got very different results from ours. The varied findings might be attributable to many factors, such as the different study populations, different pollution compositions and concentrations range, different end-points examined, and most of all, the inadequate statistical approaches and less statistical power to detect interaction. In the above mentioned studies, three of them chose the 90th or 95th percentiles as cut-off points and two of them detected the interaction between PM_{10} and O_3 at very high concentrations, i.e., PM_{10} higher than 225.7μg/m^3 or O_3 higher than 228.7μg/m^3 which well exceeded the

pollution concentration range in Hong Kong and other developed countries. There is uncertainty whether effects at high concentrations will occur at lower pollutant levels normally found in ambient air.

Our findings were consistent with a study conducted in Seoul to examine the interaction between particulates and gaseous pollutants. Authors found that these pollutants are interactive with respect to their effects on the risk of stroke mortality (Hong et al. 2002)**.** The ERRs for an interquartile range increase of O_3 (32.8 μg/m^3) decreased from 5.5% to -2.5% when PM_{10} concentrations were changed from below to above the median level (67.6 μg/m^3). The relative risks for PM_{10} also depended on the different concentrations of gaseous pollutants. Another cohort study examining the effects of ambient air pollution on school absenteeism due to respiratory illness reported that the short-term effects of a 20-ppb change of O_3 on illness-related absenteeism were much greater in communities with lower levels of PM_{10} compared with communities with high levels (>=35μg/m^3 in annual mean) of PM_{10}. Authors suggested long-term exposure to elevated levels of PM_{10} decrease acute response to O_3 and PM_{10} act as effect modifier for the short-term effects of ozone (Gilliland et al. 2001). The APHENA study, bringing together data from the European APHEA and U.S. NMMAPS projects, along with Canadian data, observed a smaller PM_{10} effect on mortality among the elderly in the US cities with higher O_3 levels (Katsouyanni et al. 2009; Samoli et al. 2008). These studies might help explain our findings about the antagonistic interaction between PM_{10} and O_3.

It is biologically plausible for the interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations. The experimental data were consistent with the epidemiological evidences for the acute pulmonary effects of ozone and respirable

particulate matter and suggest a possible paracrine /endocrine disruption mechanisms induced by particles exposure (Bouthillier et al. 1998). Combined air pollution particles and ozone exposure increased airway responsiveness in mice (Goldsmith et al. 2002), $PM_{2.5}$ plus ozone impair vascular function and raised diastolic blood pressure (Brook et al. 2009), decreased heart rate variability (HRV) and led to poor cardiac autonomic function (Power et al. 2008). A study that examined the interaction between ozone and airborne particulate matter in office air (Molhave et al. 2005) found the combined exposure caused significantly more effects than either ozone exposures or dust exposures, and the effects could be measured as release of cytokines and changes of the respiratory function. Some other researchers indicated that ozone and particulate matter independently regulate the expression of lung endothelin system genes, but show complex toxicological interaction with respect to plasma endothelin ET-1, a prognostic indicator of cardiac mortality (Thomson et al. 2005). Several experimental studies also reported the synergistic interactions of ozone and respirable aerosols on rat lungs (Adamson et al. 1999; Kleinman et al. 2000; Last JA et al. 1986; Vincent et al. 1997; Warren DL and Last JA 1987; Warren DL et al. 1986, 1988).

Differences in dose and dose pattern are key caveats in extrapolating these laboratory findings to environmental exposures. Nearly all of the laboratory studies involved high concentrations that are not reflective of typical environmental exposures (Mauderly and Samet 2009). It is hard to relate different studies performed under different conditions of toxicant concentration and exposure duration. It is also hard to extrapolate the results of experimental studies to “real-life” while the exposure level is much lower and the subjects are in different sensitive characteristics. Any description of interactions is really valid only for the specific conditions of the study

in question, and cannot be generalized to all conditions of exposure to a particular pollution mixture (Schlesinger 1995).

4.4.1.2.3 Interactions between PM_{10} and SO_2 on cardiac hospitalizations

The bivariate response surfaces did not show any clear joint effect patterns for PM_{10} and SO_2 on circulatory hospitalizations (Figure-20). The greatest joint effect was the mixture when PM_{10} and SO_2 were both at high levels (Table-23). SO_2 modified the effects of PM_{10} on emergency hospital admissions for cardiac diseases (Table-24), however, evidences of PM_{10} being a modifier of the effects of SO_2 were not found (Table-25).

We used the joint effect model (Tse et al. 2011; Wang et al. 2009) by dividing each pollutant concentration into three categories and creating *PSlevel* to denote the nine different combinations of PM_{10} and SO_2 as a mixture. Using the combination of two pollutants both at the low levels as the relative none-exposure reference group, we estimated the effect of the joint exposure and the effects of the individual exposures approximately. So we could estimate the synergy occurred or not by comparing the joint effect with the sum of the individual effects. We found the effects of combined exposure to PM_{10} and SO_2 were higher than the sum of individual effects on emergency hospital admissions for CIR, HD and IHD, with the synergy indices all higher than 1, showing some synergistic interactions between PM_{10} and SO_2 for cardiac hospitalizations. Further analysis using parametric stratified model showed the modified effects of SO_2 on PM_{10} (Table-24), providing some more evidences of the synergy between PM_{10} and SO_2 on emergency hospital admissions for cardiac diseases.

Many epidemiological studies have confirmed the adverse effects of PM_{10} and SO_2 on cardiovascular mortality and morbidity. However, few epidemiological studies examined the interactions between PM_{10} and SO_2 and the evidences are quite inadequate and controversial (Hong et al. 2002; Spix and Wichmann 1996; Touloumi et al. 1996; Vigotti et al. 1996; Zmirou et al. 1996). The study conducted in Seoul examined the interaction between particulates and gaseous pollutants on stroke mortality (Hong et al. 2002). Authors reported the ERR for each interquartile range in SO_2 increased from 1.3% to 3.8% when PM_{10} concentrations were changed from below to above the median level (67.6 $\mu g/m^3$) in the model. At the same time, the ERR for PM_{10} decreased from 1.7% to 0.5% when SO_2 concentrations were changed from below to above the median level (17.8 $\mu g/m^3$). Authors drew the conclusion that PM_{10} and gaseous pollutants were interactive with respect to their effects on the risk of stroke mortality**.** However, it seems inconsistent about the direction of the interaction in this study. Several APHEA studies in Europe identified some interactions between particulate matter and SO_2. A study in Lyon, France found when PM_{13} concentrations were greater than 60 $\mu g/m^3$, the joint SO_2 effects on mortality were increased (Zmirou et al. 1996). A study in Athens, Greece observed a stronger effect of SO_2 on daily total mortality when the levels of BS were higher than 100$\mu g/m^3$ (Touloumi et al. 1996). A study in Milan, Italy found the effects of TSP on respiratory hospital admissions were stronger when SO_2 was higher than 100$\mu g/m^3$, and the effects of SO_2 were stronger when TSP was higher than 100$\mu g/m^3$ (Vigotti et al. 1996). These three European studies suggested some synergy between particulates matter and SO_2 on mortality or hospital admissions. However, another APHEA study conducted in Koln, Germany got the opposite findings. Authors reported that the effects of SO_2 on daily total mortality were stronger when TSP was below 100$\mu g/m^3$ or PM_7 was below 60$\mu g/m^3$. The effects of particles also tended to be stronger when

daily mean SO_2 was below 100μg/m^3, suggesting some antagonism (Spix and Wichmann 1996). The interactions between PM and SO_2 were inconsistent and controversial. Moreover, these four APHEA studies used data almost twenty years ago. During that period from 1975 to 1990, the median value of SO_2 for several APHEA cities was around 60μg/m^3 which was much higher than that in other developed countries nowadays.

The underlying mechanisms linking air pollutants to increased cardiovascular risk have been studied. An investigation showed that short-term exposure to air pollution is associated with changes in the global coagulation function and suggested a tendency towards hypercoagulability, which might contribute to trigger cardiovascular events (Baccarelli et al. 2007). Some other researchers suggested that higher PM_{10} and gaseous pollution concentrations are associated with impaired cardiac autonomic control (Liao et al. 2004) and systemic inflammation (Thompson et al. 2010), and highlighted the putative mechanisms through which air pollution is associated with cardiovascular diseases. Vehicle derived inhaled SO_2 exposure was found to likely reduce cardiac vagal control, a response that would be expected to increase susceptibility to ventricular arrhythmia (Routledge et al. 2006). Nemmar et al. found that the smallest particles could even translocate from the lungs into the circulation and thus influence cardiovascular endpoints more directly (Nemmar et al. 2002). However, the mechanisms underlying specific interaction between PM_{10} and SO_2 are not very clear. Mechanisms through the physical adsorption and chemical reaction in the exposure atmosphere or on a particle surface, or through the alteration of the pulmonary environment were suggested to explain the interactions between particles and gaseous pollutants (Schlesinger 1995). Kleinman reported there was a slight tendency for human respiratory symptoms of both upper and lower airway to

be greater during the exposure to the mixture of SO_2, NO_2 and airborne particulate matter, suggesting some interactions between these pollutants (Kleinman et al. 1985).

We recognize that air pollution exists as a complex mixture and that effects attributed to PM_{10}, O_3, NO_2 or SO_2 may be influenced by the underlying toxicity of the full mixture of all air pollutants. These pollutants are further transformed by processes in the atmosphere. For example, ground level ozone is a secondary pollutant produced by the interaction of sunlight with nitrogen dioxide and volatile organic compounds. In addition, NO_2 and other nitrogen oxides also contribute to the generation of ozone and other oxidant pollutants; NO_2 and SO_2 are precursors of the formation of nitric / sulfuric acid and subsequently the nitrate/sulfate components of PM. These secondary nitrates and sulfates contribute to the toxicity of cardiovascular effects of PM (Ito et al. 2011; Ostro et al. 2008). The observed synergetic interactions between PM_{10} and NO_2 / SO_2 on cardiovascular diseases or the antagonistic interaction between PM_{10} and O_3 on cardio-respiratory diseases in this study might be due to the different PM_{10} components across different levels of gaseous pollutants, which needs to be further studied.

4.4.2 Strengths and limitations of this study

There are two major strengths in this study. Firstly, to our knowledge, this study is the largest single city study to date examining the joint effects of PM_{10} and gaseous pollutants on emergency hospital admissions for cardio-respiratory diseases, with over 1.4 million hospital admissions spreading over a period of 10 years. We used multiple health end-points of respiratory and circulatory diseases, which were abstracted from the reliable central-computerized source of hospital admission data for over 90% of the population in Hong Kong and found the synergy between PM_{10}

and NO_2 or SO_2 occurred on emergency cardiac hospitalizations. We also found the antagonism between PM_{10} and ozone on emergency cardio-respiratory admissions. Secondly, we performed three parallel time series approaches to examine the joint effects and interactions, which produced consistent results and strengthened the validity of our findings. It was the first time that we introduced the joint effect model into the time series air pollution study, which was commonly used in the traditional epidemiological studies to examine interaction, by calculating the synergy indices to estimate whether the synergy or antagonism occurred or not.

However, some key limitations should also be noted. Firstly, caution is needed to interpret any time series studies within a single location. This study was conducted in Hong Kong with a subtropical climate. Compared with the Global Air Quality Guidelines set by World Health Organization (50 $\mu g/m^3$ for 24- hour mean of PM_{10}, 40 $\mu g/m^3$ for annual mean of NO_2, 20 $\mu g/m^3$ for 24- hour mean of SO_2, and 100 $\mu g/m^3$ for 8- hour mean of O_3) (WHO, 2005), the PM_{10} and NO_2 level in Hong Kong was quite high. During our study period from 1998 to 2007, nearly half of the days (46.1%) recorded PM_{10} concentrations higher than 50 $\mu g/m^3$, 80.1% of days had NO_2 concentrations higher than 40 $\mu g/m^3$ and 36.3% of days had SO_2 concentrations higher than 20 $\mu g/m^3$, while only 2.3% of days recorded O_3 concentrations higher than 100 $\mu g/m^3$. The results of this study may not be generalized to other places with different pollution compositions and concentration range. Secondly, we chose tertiles as the cutoff points, considering the statistical power and choosing a relatively low exposure reference group. Although we also tried quartiles or quintiles as cutoff points and got similar results (data not shown), choice of cutoff points was still somewhat arbitrary and might not reflect the underlying biological mechanisms. Thirdly, we used the same lag_0 exposure for all pollutants while examining the

interaction. However, the effects of the ambient pollution on different subsets of the cardio-respiratory outcomes might involve different lags, and this could underestimate the true interaction. Fourthly, as an ecological time series study, bias from exposure misclassification due to the lack of individual exposure measurement might reduce the opportunity to detect the interaction or distort interaction assessment. Finally, we estimated the joint effects of the PM_{10} and the gaseous pollutants one at one time and ignored the effects from other gaseous pollutants. Air pollution including particulate matter and gaseous pollutants as a complex mixture should be further studied.

4.5 Conclusion and recommendations

In conclusion, we found synergistic interactions between PM_{10} and NO_2 or SO_2 on emergency cardiac hospitalizations in Hong Kong. We also found antagonistic interactions between PM_{10} and O_3 on cardio-respiratory hospitalizations, and possible antagonism between PM_{10} and NO_2 on COPD admissions. These findings may have important implications in the assessment of the adverse effects of air pollutants and contribute to the development of a foundation for multi-pollutant air quality management. Intuitively, people believe that the harmful effects of air pollutants should be additive, environmental authorities in some countries, e.g. Canada, France (Cairncross et al. 2007; Sicard et al. 2011, 2012) have adopted so called 'Aggregate Risk Index' for risk assessment and risk communication. Findings on interactions in the present study should call for a review on the validity of such a conventional/intuitive approach. However, it is necessary to determine whether a consistent finding could be found in other settings. Experimental studies are also needed to test the interactions between PM_{10} and gaseous pollutants at low concentrations similar to environmental exposures in modern cities, and to explore the underlying mechanisms involved.

Chapter 5 Concluding remarks

Particulate matter pollution is a great public concern for its extensive adverse effects on population health. Only in recent years have researchers begun to separately address the health effects of the coarse particles, because PM_c were initially considered as potentially less toxic than fine particles and the PM_c measurement data were scarce. In this series of studies related to particulate air pollutants, we conducted time series analyses to estimate the differential effects of $PM_{2.5}$ and PM_c simultaneously on emergency hospital admissions for respiratory and circulatory diseases in Hong Kong, after adjusted for all time varying confounders and taking into account the gaseous pollutants. We found significantly positive associations with both $PM_{2.5}$ and PM_c on respiratory diseases and the much stronger and significantly positive associations with $PM_{2.5}$ than PM_c on cardiac diseases. Our findings added to the growing body of literature about the adverse health effects of PM_c and the different health effects of the two fractions of PM_{10}.

Air pollution is a complex mixture of particles and gaseous pollutants. Multipollutant approach to quantify the health consequences of air pollution mixture as a whole requires an understanding of the joint effects or interaction between pollutants. The evidence from epidemiological studies in the literature about the interaction between PM_{10} and gaseous pollutants was quite inadequate and inconclusive. In the present series of studies, we used three time series approaches (bivariate response surface model, joint effect model and parametric stratified model) to examine the joint effects of PM_{10} and gaseous pollutants one by one. We found synergistic interactions between PM_{10} and NO_2 or SO_2 on emergency cardiac hospitalizations in Hong Kong. We also found antagonistic interactions between PM_{10} and O_3 on cardio-respiratory

hospitalizations, and possible antagonism between PM_{10} and NO_2 on COPD admissions.

These findings provide supportive evidence for separately regulating PM_c in the future and contribute to the development of a multi-pollutant air quality risk assessment and management system. Current air quality health risk assessment in Hong Kong uses the air pollution index (API) that assumes health effects from the single-pollutant model. Our findings on interactions in the present study suggested that multi-pollutant model should be better than this conventional/intuitive approach. Future studies are needed to elucidate the toxicological differences linked to the different chemical compositions of PM_{10} across different gaseous pollutant levels, and to set up an appropriate multi-pollutant prediction model which takes into consideration the effects of particulate matter and gaseous pollutants as a mixture.

References List

Adamson IYR, Vincent R, Bjarnason SG. 1999. Cell injury and interstitial inflammation in rat lung after inhalation of ozone and urban particulates. American Journal of Respiratory Cell and Molecular Biology 20:1067-1072.

Aga E, Samoli E, Touloumi G, Anderson HR, Cadum E, Forsberg B, Goodman P, Goren A, Kotesovec F, Kriz B , Macarol-Hiti M, Medina S, Paldy A, Schindler C, Sunyer J, Tittanen P, Wojtyniak B, Zmirou D, Schwartz J, Katsouyanni K. 2003. Short-term effects of ambient particles on mortality in the elderly: results from 28 cities in the APHEA2 project. European Respiratory Journal 21:28S-33S.

Almeida SM, Pio CA, Freitas MC, Reis MA, Trancoso MA . 2006. Approaching PM2.5 and PM2.5-10 source apportionment by mass balance analysis, principal component analysis and particle size distribution. Science of the Total Environment 368:663-674.

Anderson HR, Atkinson RW, Peacock JL, Sweeting MJ, Marston L. 2005. Ambient particulate matter and health effects - Publication bias in studies of short-term associations. Epidemiology 16:155-163.

Anderson HR, Bremner SA, Atkinson RW, Harrison RM, Walters S. 2001. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. Occupational and Environmental Medicine 58:504-510.

Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. 2001. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air Pollution and Health: a European Approach. American Journal of Respiratory and Critical Care Medicine 164:1860-1866.

Atkinson RW, Fuller GW, Anderson HR, Harrison RM, Armstrong B. 2010. Urban Ambient Particle Metrics and Health A Time-series Analysis. Epidemiology 21:501-511.

Atkinson RW. 2004. Acute effects of air pollution on admissions: reanalysis of APHEA 2. American Journal of Respiratory and Critical Care Medicine 169:1257-1258.

Baccarelli A, Zanobetti A, Martinelli I, Grillo P, Hou L, Giacomini S, Bonzini M, Lanzani G, Mannucci PM, Bertazzi PA, Schwartz J. 2007. Effects of exposure to air pollution on blood coagulation. Journal of Thrombosis and Haemostasis 5:252-260.

Bell ML, Dominici F, Samet JM. 2005. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. Epidemiology 16:436-445.

Bell ML, Ebisu K, Peng RD, Walker J, Samet JM, Zeger SL, Dominici F. 2008. Seasonal and Regional Short-term Effects of Fine Particles on Hospital Admissions in 202 US Counties, 1999-2005. American Journal of Epidemiology 168:1301-1310.

Bell ML, Samet JM, Dominici F. 2004. Time-series studies of particulate matter. Annual Review of Public Health 25:247-280.

Boren HG. 1964. Carbon as a carrier mechanism for irritant gases. Archives of Environmental Health 8:119-124.

Bouthillier L, Vincent R, Goegan P, Adamson IYR, Bjarnason S, Stewart M, Guenette J, Potvin M, Kumarathasan P. 1998. Acute effects of inhaled urban particles and ozone - Lung morphology, macrophage activity, and plasma endothelin-1. American Journal of Pathology 153:1873-1884.

Braga ALF, Zanobetti A, Schwartz J. 2001. The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities. Journal of Occupational and Environmental Medicine 43:927-933.

Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, Morishita M, Marsik FJ, Kamal AS, Kaciroti N, Harkema J, Corey P, Silverman F, Gold DR, Wellenius G, Mittleman MA, Rajagopalan S, Brook JR. 2009. Insights Into the Mechanisms and Mediators of the Effects of Air Pollution Exposure on Blood Pressure and Vascular Function in Healthy Humans. Hypertension 54:659-667.

Brunekreef B, Forsberg B. 2005. Epidemiological evidence of effects of coarse airborne particles on health. European Respiratory Journal 26:309-318.

Burnett RT, Cakmak S, Brook JR, Krewski D. 1997. The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environmental Health Perspectives 105:614-620.

Burnett RT, Smith-Doiron M, Stieb D, Cakmak S, Brook JR. 1999. Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Archives of Environmental Health 54:130-139.

Chang HH, Peng RD, Dominici F. 2011. Estimating the acute health effects of coarse particulate matter accounting for exposure measurement error. Biostatistics 12:637-652.

Chen GH, Song GX, Jiang LL, Zhang YH, Zhao NQ, Chen BH, Kan HD. 2007. Interaction between ambient particles and ozone and its effect on daily mortality. Biomedical and Environmental Sciences 20:502-505.

Chen RJ, Li Y, Ma YJ, Pan GW, Zeng G, Xu XH, Chen BH, Kan HD. 2011. Coarse particles and mortality in three Chinese cities: The China Air Pollution and Health Effects Study (CAPES). Science of the Total Environment 409:4934-4938.

Chen Y, Yang QY, Krewski D, Burnett RT, Shi YL, McGrail KM. 2005. The effect of coarse ambient particulate matter on first, second, and overall hospital admissions for respiratory disease among the elderly. Inhalation Toxicology 17:649-655.

Chen Y, Yang QY, Krewski D, Shi Y, Burnett RT, McGrail K. 2004. Influence of relatively low level of particulate air pollution on hospitalization for COPD in elderly people. Inhalation Toxicology 16:21-25.

Diociaiuti M, Balduzzi M, De Berardis B, Cattani G, Stacchini G, Ziemacki G, Marconi A, Paoletti L. 2001. The two PM2.5 (fine) and PM2.5-10 (coarse) fractions: Evidence of different biological activity. Environmental Research 86:254-262.

Dockery DW. 2009. Health effects of particulate air pollution. Annals of Epidemiology 19:257-263.

Dominici F, Peng RD, Barr CD, Bell ML. 2010. Protecting Human Health From Air Pollution Shifting From a Single-pollutant to a Multipollutant Approach. Epidemiology 21:187-194.

Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA-Journal of the American Medical Association 295:1127-1134.

Englert N. 2004. Fine particles and human health--a review of epidemiological studies. Toxicology Letters 149:235-242.

Figueiras A, Domenech-Massons JM, Cadarso C. 1998. Regression models: Calculating the confidence interval of effects in the presence of interactions. Statistics in Medicine 17:2099-2105.

Fung KY, Khan S, Krewski D, Chen Y. 2006. Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. Inhalation Toxicology 18:1005-1011.

Cairncross EK, John J, Zunckel M. 2007. A novel air pollution index based on the relative risk of daily mortality associated with short-term exposure to common air pollutants. Atmospheric Environment 41:8442-8454.

Gilliland FD, Berhane K, Rapaport EB, Thomas DC, Avol E, Gauderman WJ, London SJ, Margolis HG, McConnell R, Islam KT, Peters JM. 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. Epidemiology 12:43-54.

Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R. 2000. Ambient pollution and heart rate variability. Circulation 101:1267-1273.

Goldsmith CAW, Ning YY, Qin GZ, Imrich A, Lawrence J, Murthy GGK, Catalano PJ, Kobzik L. 2002. Combined air pollution particle and ozone exposure increases airway responsiveness in mice. Inhalation Toxicology 14:325-347.

Halonen JI, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J. 2008. Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax 63:635-641.

Halonen JI, Lanki T, Yli-Tuomi T, Tiittanen P, Kulmala M, Pekkanen J. 2009. Particulate Air Pollution and Acute Cardiorespiratory Hospital Admissions and Mortality Among the Elderly. Epidemiology 20:143-153.

Hong YC, Lee JT, Kim H, Ha EH, Schwartz J, Christiani DC. 2002. Effects of air pollutants on acute stroke mortality. Environmental Health Perspectives 110:187-191.

Host S, Larrieu S, Pascal L, Blanchard M, Declercq C, Fabre P, Jusot JF, Chardon B, Le Tertre A, Wagner V, Prouvost H, Lefranc A. 2008a. Short-term associations between fine and coarse particles and hospital admissions for cardiorespiratory diseases in six French cities. Occupational and Environmental Medicine 65:544-551.

Hu W, Mengersen K, McMichael A, Tong S. 2008. Temperature, air pollution and total mortality during summers in Sydney, 1994-2004. International Journal of Biometeorology 52:689-696.

Ilabaca M, Olaeta I, Campos E, Villaire J, Tellez-Rojo MM, Romieu I. 1999. Association between levels of fine particulate and emergency visits for pneumonia and other respiratory illnesses among children in Santiago, Chile. Journal of the Air & Waste Management Association 49:154-163.

Ito, K. 2003. Association of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Health Effects Institute, Special Report. Revised analyses of time-series studies of air pollution and health. 143-156.

Ito K, Mathes R, Ross Z, Nádas A, Thurston G, Matte T. 2011. Fine particulate matter constituents associated with cardiovascular hospitalizations and mortality in New York City. Environmental Health Perspectives 119:467-473.

Jimenez E, Linares C, Martinez D, Diaz J. 2011. Particulate air pollution and short-term mortality due to specific causes among the elderly in Madrid (Spain): seasonal differences. International Journal of Environmental Health Research 21:372-390.

Kampa M, Castanas E. 2008. Human health effects of air pollution. Environmental Pollution 151:362-367.

Kan HD, London SJ, Chen GH, Zhang YH, Song GX, Zhao NQ, Jiang LL, Chen BH. 2007. Differentiating the effects of fine and coarse particles on daily mortality in Shanghai, China. Environment International 33:376-384.

Kan HD, Wong CM, Vichit-Vadakan N, Qian ZM. 2010. Short-term association between sulfur dioxide and daily mortality: The Public Health and Air Pollution in Asia (PAPA) study. Environmental Research 110:258-264.

Katsouyanni K, Samet JM, Anderson HR, Atkinson R, Le Tertre A, Medina S, Samoli E, Touloumi G, Burnett RT, Krewski D, Ramsay T, Dominici F, Peng RD, Schwartz J, and Zanobetti A; HEI Health Review Committee. 2009. Air Pollution and Health: A European and North American Approach (APHENA). Health Effects Institute Report Number 142. Boston, MA, Health Effects Institute.

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopolis Y, Rossi G, Zmirou D, Ballester F, Boumghar A, Anderson HR, Wojtyniak B, Paldy A, Braunstein R, Pekkanen J, Schindler C, Schwartz J. 2001. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology 12:521-531.

Kleinman MT, Bailey RM, Whynot JD, Anderson KR, Linn WS, Hackney JD. 1985. Controlled exposure to a mixture of SO2, NO2, and particulate air pollutants: effects on human pulmonary function and respiratory symptoms. Archives of Environmental Health 40:197-201.

Kleinman MT, Bufalino C, Rasmussen R, Hyde D, Bhalla DK, Mautz WJ. 2000. Toxicity of chemical components of ambient fine particulate matter (PM 2.5) inhaled by aged rats. Journal of Applied Toxicology 20:357-364.

Ko FWS, Tam W, Wong TW, Chan DPS, Tung AH, Lai CKW, Hui DSC. 2007a. Temporal relationship between air pollutants and hospital admissions for chronic obstructive pulmonary disease in Hong Kong. Thorax 62:780-785.

Ko FWS, Tam W, Wong TW, Lai CKW, Wong GWK, Leung TF, Ng SSS, Hui DSC. 2007b. Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. Clinical and Experimental Allergy 37:1312-1319.

Last JA, Hyde DM, Guth DJ, Warren DL. 1986. Synergistic interaction of ozone and respirable aerosols on rat lungs. I. Importance of aerosol acidity. Toxicology 39:247-257.

Last JA, Warren DL. 1987. Synergistic interaction between nitrogen dioxide and respirable aerosols of sulfuric acid or sodium chloride on rat lungs. Toxicology and Applied Pharmacology 90:34-42.

Le Tertre A, Medina S, Samoli E, Forsberg B, Michelozzi P, Boumghar A, Vonk JM, Bellini A, Atkinson R, Ayres JG, Sunyer J, Schwartz J, Katsouyanni K. 2002. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. Journal of Epidemiology and Community Health 56:773-779.

Le Tertre A, Medina S, Samoli E, Forsberg B, Michelozzi P, Boumghar A, Vonk JM, Bellini A, Atkinson R, Ayres JG, Sunyer J, Schwartz J, Katsouyanni K. 2002. Short-term effects of particulate air pollution on cardiovascular diseases in eight European cities. Journal of Epidemiology and Community Health 56:773-779.

Lee SL, Wong WHS, Lau YL. 2006. Association between air pollution and asthma admission among children in Hong Kong. Clinical and Experimental Allergy 36:1138-1146.

Levy JI, Hammitt JK, Spengler JD. 2000. Estimating the mortality impacts of particulate matter: What can be learned from between-study variability? Environmental Health Perspectives 108:109-117.

Liao DP, Duan YK, Whitsel EA, Zheng ZJ, Heiss G, Chinchilli VM, Lin HM. 2004. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: A population-based study. American Journal of Epidemiology 159:768-777.

Lin M, Chen Y, Burnett RT, Villeneuve PJ, Krewski D. 2002. The influence of ambient coarse particulate matter on asthma hospitalization in children:

Case-crossover and time-series analyses. Environmental Health Perspectives 110:575-581.

Lin M, Stieb DM, Chen Y. 2005. Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: A case-crossover analysis. Pediatrics 116:E235-E240.

Linares C, Diaz J. 2010. Short-term effect of PM2.5 on daily hospital admissions in Madrid (2003-2005). International Journal of Environmental Health Research 20:129-140.

Lippmann M, Ito K, Nadas A, Burnett RT. 2000. Association of particulate matter components with daily mortality and morbidity in urban populations. Research report (Health Effects Institute) 95:5-72.

Lipsett M, Hurley S, Ostro B. 1997. Air pollution and emergency room visits for asthma in Santa Clara County, California. Environmental Health Perspectives 105:216-222.

Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. 2001. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. Circulation 104:986-991.

Malig BJ, Ostro BD. 2009. Coarse particles and mortality: evidence from a multi-city study in California. Occupational and Environmental Medicine 66:832-839.

Mallone S, Stafoggia M, Faustini A, Gobbi GP, Marconi A, Forastiere F. 2011. Saharan Dust and Associations between Particulate Matter and Daily Mortality in Rome, Italy. Environmental Health Perspectives 119:1409-1414.

Mauderly JL, Samet JM. 2009. Is There Evidence for Synergy Among Air Pollutants in Causing Health Effects? Environmental Health Perspectives 117:1-6.

Metzger KB, Tolbert PE, Klein M, Peel JL, Flanders WD, Todd K, Mulholland JA, Ryan PB, Frumkin H. 2004. Ambient air pollution and cardiovascular emergency department visits. Epidemiology 15:46-56.

Molhave L, Kjaergaard SK, Sigsgaard T, Lebowitz M. 2005. Interaction between ozone and airborne particulate matter in office air. Indoor Air 15:383-392.

Monn C. 2001. Exposure assessment of air pollutants: a review on spatial heterogeneity and indoor/outdoor/personal exposure to suspended particulate matter, nitrogen dioxide and ozone. Atmospheric Environment 35:1-32.

Morris RD, Naumova EN. 1998. Carbon monoxide and hospital admissions for congestive heart failure: evidence of an increased effect at low temperatures. Environmental Health Perspectives 106:649-653.

Morris RD. 2001. Airborne particulates and hospital admissions for cardiovascular disease: A quantitative review of the evidence. Environmental Health Perspectives 109:495-500.

Nemmar A, Hoet PHM, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H , Mortelmans L, Nemery B. 2002. Passage of inhaled particles into the blood circulation in humans. Circulation 105:411-414.

Norris G, YoungPong SN, Koenig JQ, Larson TV, Sheppard L, Stout JW. 1999. An association between fine particles and asthma emergency department visits for children in Seattle. Environmental Health Perspectives 107:489-493.

Ostro BD, Feng WY, Broadwin R, Malig BJ, Green RS, Lipsett MJ. 2008. The impact of components of fine particulate matter on cardiovascular mortality in susceptible subpopulations. Occupational and Environmental Medicine 65:750-756.

Peng RD, Chang HH, Bell ML, McDermott A, Zeger SL, Samet JM, Dominici F. 2008. Coarse particulate matter air pollution and hospital admissions for cardiovascular and respiratory diseases among medicare patients. JAMA-Journal of the American Medical Association 299:2172-2179.

Peng RD, Dominici F, Louis TA. 2006. Model choice in time series studies of air pollution and mortality. Journal of the Royal Statistical Society Series A-Statistics in Society 169:179-198.

Perez L, Medina-Ramon M, Kunzli N, Alastuey A, Pey J, Perez N, Garcia R, Tobias A, Querol X, Sunyer J. 2009. Size Fractionate Particulate Matter, Vehicle Traffic,

and Case-Specific Daily Mortality in Barcelona, Spain. Environmental Science & Technology 43:4707-4714.

Perez L, Tobias A, Querol X, Kunzli N, Pey J, Alastuey A, Viana M, Valero N, Gonzalez-Cabre M, Sunyer J. 2008. Coarse Particles From Saharan Dust and Daily Mortality. Epidemiology 19:800-807.

Ponka A, Savela M, Virtanen M. 1998. Mortality and air pollution in Helsinki. Archives of Environmental Health 53:281-286.

Pope CA. 2009. The Expanding Role of Air Pollution in Cardiovascular Disease Does Air Pollution Contribute to Risk of Deep Vein Thrombosis? Circulation 119:3050-3052.

Power KL, Balmes J, Solomon C. 2008. Controlled Exposure to Combined Particles and Ozone Decreases Heart Rate Variability. Journal of Occupational and Environmental Medicine 50:1253-1260.

Pozzi R, De Berardis B, Paoletti L, Guastadisegni C. 2003. Inflammatory mediators induced by coarse (PM2.5-10) and fine (PM2.5) urban air particles in RAW 264.7 cells. Toxicology 183:243-254.

Ren C, Williams GM, Mengersen K, Morawska L, Tong S. 2008a. Does temperature modify short-term effects of ozone on total mortality in 60 large eastern US communities? An assessment using the NMMAPS data. Environment International 34:451-458.

Ren C, Williams GM, Morawska L, Mengersen K, Tong S. 2008b. Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data. Occupational and Environmental Medicine 65:255-260.

Ren CZ, Tong SL. 2006. Temperature modifies the health effects of particulate matter in Brisbane, Australia. International Journal of Biometeorology 51:87-96.

Ren CZ, Williams GM, Mengersen K, Morawska L, Tong SL. 2009. Temperature Enhanced Effects of Ozone on Cardiovascular Mortality in 95 Large US Communities, 1987-2000: Assessment Using the NMMAPS Data. Archives of Environmental & Occupational Health 64:177-184.

Ren CZ, Williams GM, Tong SL. 2006. Does particulate matter modify the association between temperature and cardiorespiratory diseases? Environmental Health Perspectives 114:1690-1696.

Revich B, Shaposhnikov D. 2010. The effects of particulate and ozone pollution on mortality in Moscow, Russia. Air quality, atmosphere, & health 3:117-123.

Roberts S. 2004. Interactions between particulate air pollution and temperature in air pollution mortality time series studies. Environmental Research 96:328-337.

Rothman KJ, Greenland S, Lash TL. 2008. Concepts of Interaction. *Modern epidemiology*. Philadelphia: Lippincott Williams and Wilkins. p71-83.

Routledge HC, Manney S, Harrison RM, Ayres JG, Townend JN. 2006. Effect of inhaled sulphur dioxide and carbon particles on heart rate variability and markers of inflammation and coagulation in human subjects. Heart 92:220-227.

Sacks JD, Stanek LW, Luben TJ, Johns DO, Buckley BJ, Brown JS, Ross M. 2011. Particulate Matter-Induced Health Effects: Who Is Susceptible? Environmental Health Perspectives 119:446-454.

Samet JM, Dominici F, Curriero FC, Coursac I, Zeger SL. 2000. Fine particulate air pollution and mortality in 20 US Cities, 1987-1994. New England Journal of Medicine 343:1742-1749.

Samoli E, Peng R, Ramsay T, Pipikou M, Touloumi G, Dominici F, Burnett R, Cohen A, Krewski D, Samet J, Katsouyanni K. 2008. Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. Environmental Health Perspectives 116:1480-1486.

Scaife A, Barclay J, Hillis GS, Srinivasan J, Macdonald DW, Ross JA, Ayres JG. 2012. Lack of effect of nitrogen dioxide exposure on heart rate variability in patients with stable coronary heart disease and impaired left ventricular systolic function. Occupational and Environmental Medicine 69:587-591.

Schlesinger RB. 1995. Interaction of gaseous and particulate pollutants in the respiratory tract: Mechanisms and modulators. Toxicology 105:315-325.

Schwartz J, Neas LM. 2000. Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology 11:6-10.

Schwartz J, Sarnat JA, Coull BA, Wilson WE. 2007. Effects of exposure measurement error on particle matter epidemiology: a simulation using data from a panel study in Baltimore, MD. Journal of Exposure Science and Environmental Epidemiology 17:S2-S10.

Schwartz J, Spix C, Touloumi G, Bacharova L, Barumamdzadeh T, leTertre A, Piekarksi T, deLeon AP, Ponka A, Rossi G, Saez M, Schouten JP. 1996. Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. Journal of Epidemiology and Community Health 50:S3-S11.

Schwartz J. 2001. Air pollution and blood markers of cardiovascular risk. Environmental Health Perspectives 109:405-409.

Shi T, Knaapen AM, Begerow J, Birmili W, Borm PJA, Schins RPF. 2003. Temporal variation of hydroxyl radical generation and 8-hydroxy-2 '-deoxyguanosine formation by coarse and fine particulate matter. Occupational and Environmental Medicine 60:315-321.

Sicard P, Lesne O, Alexandre N, Mangin A, Collomp R. 2011. Air quality trends and potential health effects - Development of an aggregate risk index. Atmospheric Environment. 45:1145-1153.

Sicard P, Talbot C, Lesne O, Mangin A, Alexandre N, Collomp, R. 2012. The Aggregate Risk Index: An intuitive tool providing the health risks of air pollution to health care community and public. Atmospheric Environment 46:11-16.

Simpson RW, Williams G, Petroeschevsky A, Morgan G, Rutherford S. 1997. Associations between outdoor air pollution and daily mortality in Brisbane, Australia. Archives of Environmental Health 52:442-454.

Slaughter JC, Kim E, Sheppard L, Sullivan JH, Larson TV, Claiborn C. 2005. Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. Journal of Exposure Analysis and Environmental Epidemiology 15:153-159.

Spix C, Wichmann HE. 1996. Daily mortality and air pollutants: findings from Koln, Germany. Journal of Epidemiology and Community Health 50 (Suppl 1):s52-s58.

Sunyer J, Atkinson R, Ballester F, Le Tertre A, Ayres JG, Forastiere F, Forsberg B, Vonk JM, Bisanti L, Anderson RH, Schwartz J, Katsouyanni K. 2003. Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the APHEA 2 study. Occupational and Environmental Medicine 60:e2.

Sunyer J, Basagana X. 2001. Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. International Journal of Epidemiology 30:1138-1140.

Tam WW, Wong TW, Wong AH, Hui DS. 2012a. Effect of dust storm events on daily emergency admissions for respiratory diseases. Respirolory 17:143-148.

Tam WW, Wong TW, Wong AH. 2012b. Effect of dust storm events on daily emergency admissions for cardiovascular diseases. Circulation Journal 76:655-660.

Tecer LH, Alagha O, Karaca F, Tuncel G, Eldes N. 2008. Particulate matter (PM2.5, PM10-2.5, and PM10) and children's hospital admissions for asthma and respiratory diseases: A bidirectional case-crossover study. Journal of Toxicology and Environmental Health-Part A-Current Issues 71:512-520.

Tellez-Rojo MM, Romieu I, Ruiz-Velasco S, Lezana MA, Hernandez-Avila MM. 2000. Daily respiratory mortality and PM10 pollution in Mexico City: importance of considering place of death. European Respiratory Journal 16:391-396.

Thach TQ, Wong CM, Chan KP, Chau YK, Thomas GN, Ou CQ, Yang L, Peiris JSM, Lam TH, Hedley AJ. 2010. Air pollutants and health outcomes: Assessment of confounding by influenza. Atmospheric Environment 44:1437-1442.

Thompson AMS, Zanobetti A, Silverman F, Schwartz J, Coull B, Urch B, Speck M, Brook JR, Manno M, Gold DR. 2010. Baseline Repeated Measures from Controlled Human Exposure Studies: Associations between Ambient Air Pollution Exposure and the Systemic Inflammatory Biomarkers IL-6 and Fibrinogen. Environmental Health Perspectives 118:120-124.

Thomson E, Kumarathasan P, Goegan P, Aubin RA, Vincent R. 2005. Differential regulation of the lung endothelin system by urban particulate matter and ozone. Toxicological Sciences 88:103-113.

Tolbert PE, Klein M, Metzger KB, Peel J, Flanders WD, Todd K, Mulholland JA, Ryan PB, Frumkin H. 2000. Interim results of the study of particulates and health in Atlanta (SOPHIA). Journal of Exposure Analysis and Environmental Epidemiology 10:446-460.

Tong HY, Cheng WY, Samet JM, Gilmour MI, Devlin RB. 2010. Differential Cardiopulmonary Effects of Size-Fractionated Ambient Particulate Matter in Mice. Cardiovascular Toxicology 10:259-267.

Touloumi G, Samoli E, Katsouyanni K. 1996. Daily mortality and "winter type" air pollution in Athens, Greece--a time series analysis within the APHEA project. Journal of Epidemiology and Community Health 50 (Suppl 1):s47-s51.

Trevor Hastie RT. 1990. Generalized additive models. London: Chapman and Hall.

Tse LA, Yu IT, Qiu H, Au JS, Wang XR. 2011. A case-referent study of lung cancer and incense smoke, smoking, and residential radon in Chinese men. Environmenal Health Perspective 119:1641-1646.

Vigotti MA, Rossi G, Bisanti L, Zanobetti A, Schwartz J. 1996. Short term effects of urban air pollution on respiratory health in Milan, Italy, 1980-89. Journal of Epidemiology and Community Health 50 Suppl 1:s71-s75.

Vincent R, Bjarnason SG, Adamson IYR, Hedgecock C, Kumarathasan P, Guenette J, Potvin M, Goegan P, Bouthillier L. 1997. Acute pulmonary toxicity of urban particulate matter and ozone. American Journal of Pathology 151:1563-1570.

Wang XR, Chiu YL, Qiu H, Au JSK, Yu ITS. 2009. The roles of smoking and cooking emissions in lung cancer risk among Chinese women in Hong Kong. Annals of Oncology 20:746-751.

Warren DL, Guth DJ, Last JA. 1986. Synergistic interaction of ozone and respirable aerosols on rat lungs. II. Synergy between ammonium sulfate aerosol and various concentrations of ozone. Toxicology and Applied Pharmacology 84:470-479.

Warren DL, Hyde DM, Last JA. 1988. Synergistic interaction of ozone and respirable aerosols on rat lungs. IV. Protection by quenchers of reactive oxygen species. Toxicology 53:113-133.

Warren DL, Last JA. 1987. Synergistic interaction of ozone and respirable aerosols on rat lungs. III. Ozone and sulfuric acid aerosol. Toxicology and Applied Pharmacology 88:203-216.

Wilson WE, Suh HH. 1997. Fine particles and coarse particles: Concentration relationships relevant to epidemiologic studies. Journal of the Air & Waste Management Association 47:1238-1249.

Wong CM, Atkinson RW, Anderson HR, Hedley AJ, Ma S, Chau PYK, Lam TH. 2002. A tale of two cities: Effects of air pollution on hospital admissions in Hong Kong and London compared. Environmental Health Perspectives 110:67-77.

Wong CM, Ma S, Hedley AJ, Lam TH. 1999. Does ozone have any effect on daily hospital admissions for circulatory diseases? Journal of Epidemiology and Community Health 53:580-581.

Wong CM, Ma S, Hedley AJ, Lam TH. 2001. Effect of air pollution on daily mortality in Hong Kong. Environmental Health Perspectives 109:335-340.

Wong CM, Ou CQ, Chan KP, Chau YK, Thach TQ, Yang L, Chung RYN, Thomas GN, Peiris JSM, Wong TW, Hedley AJ, Lam TH. 2008a. The effects of air pollution on mortality in socially deprived urban areas in Hong Kong, China. Environmental Health Perspectives 116:1189-1194.

Wong CM, Vichit-Vadakan N, Kan HD, Qian ZM. 2008b. Public Health and Air Pollution in Asia (PAPA): A multicity study of short-term effects of air pollution on mortality. Environmental Health Perspectives 116:1195-1202.

Wong GWK, Ko FWS, Lau TS, Li ST, Hui D, Pang SW, Leung R, Fok TF, Lai CKW. 2001. Temporal relationship between air pollution and hospital admissions for asthmatic children in Hong Kong. Clinical and Experimental Allergy 31:565-569.

Wong TW, Lau TS, Yu TS, Neller A, Wong SL, Tam W, Pang SW. 1999. Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. Occupational and Environmental Medicine 56:679-683.

Wong TW, Tam W, Yu ITS, Wun YT, Wong AHS, Wong CM. 2006. Association between air pollution and general practitioner visits for respiratory diseases in Hong Kong. Thorax 61:585-591.

Wong TW, Tam WS, Yu TS, Wong AH. 2002. Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. Occupational and Environmental Medicine 59:30-35.

World Health Organization. 1975. International Statistical Classification of Diseases, Injuries, and Causes of Death. 9th Revision. Geneva: World Health Organization.

World Health Organization. 2005. WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide, and sulfur dioxide. Available [accessed 6 June, 2012]: http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf

Zanobetti A, Schwartz J, Samoli E, Gryparis A, Touloumi G, Atkinson R, Le Tertre A, Bobros J, Celko M, Goren A, Forsberg B, Michelozzi P, Rabczenko D, Aranguez RE, Katsouyanni K. 2002. The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. Epidemiology 13:87-93.

Zanobetti A, Schwartz J. 2009. The Effect of Fine and Coarse Particulate Air Pollution on Mortality: A National Analysis. Environmental Health Perspectives 117:898-903.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, Cohen A. 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environmental Health Perspectives 108:419-426.

Zmirou D, Barumandzadeh T, Balducci F, Ritter P, Laham G, Ghilardi JP. 1996. Short term effects of air pollution on mortality in the city of Lyon, France, 1985-90. Journal of Epidemiology and Community Health 50 (Suppl 1):S30-S35.

Appendix – Relevant Publications and Submitted/Drafted Papers

1. Qiu H, Yu ITS, Tian LW, Wang XR, Tse LA, Tam W, Wong TW. 2012. Effects of Coarse Particulate Matter on Emergency Hospital Admissions for Respiratory Diseases: A Time Series Analysis in Hong Kong. ***Environmental Health Perspectives*** 120:572-576.

2. Qiu H, Yu ITS, Wang XR, Tian LW, Tse LA, Wong TW. Season and Humidity Jointly Modified the Effects of Air Pollution on COPD Hospitalizations in Hong Kong. ***Atmospheric Environment*** 2012, DOI: 10.1016/j.atmosenv.2012.07.026. http://dx.doi.org/10.1016/j.atmosenv.2012.07.026

3. Qiu H, Yu ITS, Wang XR, Tian LW, Tse LA, Wong TW. Differential Effects of Fine and Coarse Particles on Daily Emergency Cardiovascular Hospitalizations in Hong Kong. ***Atmospheric Environment*** 2012, (In press).

4. Qiu H, Yu ITS, Wang XR, Tian LW, Tse LA, Wong TW. Cool and Dry Weather Enhances the Effects of Pollution on Emergency IHD Hospital Admissions. ***International Journal of Cardiology*** 2012, (In press).

5. Yu ITS, Qiu H, Wang XR, Tian LW, Tse LA. Synergy between Particulate Matter and Nitrogen Dioxide on Emergency Hospital Admissions for Cardiac Diseases in Hong Kong. (Submitted).

6. Interaction between Particulate Matter and Ozone Air Pollution on Emergency Cardiorespiratory Hospital Admissions in Hong Kong. (Drafted).